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| ATTORNEY DOCKET NUMBER |
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| 0887-4149US2 |

# TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

U.S. APPLICATION NO. (If known. see 37 CFR 1.51
**10/088192**

| INTERNATIONAL APPLICATION NO. PCT/US00/25156 | INTERNATIONAL FILING DATE 14 September 00 (14.09.00) | EARLIEST PRIORITY DATE CLAIMED 14 September 99 (14.09.99) |
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TITLE OF INVENTION

IMAGING OF SCATTERING MEDIA USING RELATIVE DETECTOR VALUES

APPLICANT(S) FOR DO/EO/US

Randall L. BARBOUR

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.

2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.

3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and 21 indicated below.

4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).

5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))

    a. ☐ is attached hereto (required only if not communicated by the International Bureau).
    b. ☒ has been communicated by the International Bureau.
    c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).

6. ☐ An English language translation of the International application as filed (35 U.S.C. 371(c)(2)).

    a. ☐ is attached hereto.
    b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).

7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))

    a. ☐ are attached hereto (required only if not communicated by the International Bureau).
    b. ☐ have been communicated by the International Bureau.
    c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
    d. ☒ have not been made and will not be made.

8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).

9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).

10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

**Items 11. to 16. below concern document(s) or information included:**

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98, PTO-1449 and copies of all cited references.

12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. ☐ A FIRST preliminary amendment.

14. ☐ A SECOND or SUBSEQUENT preliminary amendment.

15. ☐ A substitute specification.

16. ☐ A change of power of attorney and/or address letter.

17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 154(d)(2) with copy of Statement Under 37 CFR Section 1.821(f) and WIPO Standard ST.25 as filed with the International Bureau of WIPO.

18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).

19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).

687236 v1

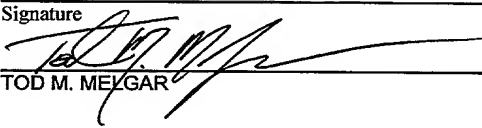| APPLICATION NO. (if known, see 37 C.F.R. 1.51) | INTERNATIONAL APPLICATION NO. | ATTORNEY'S DOCKET NO. |
|---|---|---|
| TBA<br>**10/088192** | PCT/US00/25156 | 0887-4149US2 |

20.  ☒  Other items or information:

- Copy of published PCT application, Publication Number WO 01/20546, published on 22 March 2001;
- Copy of Search report;
- Copy of International Preliminary Examination report with Notification of Transmittal; and
- Copy of Notification of Change in Abstract as Previously Established by ISA.

687236 v1

| U.S. APPLICATION NO. (if known, see 37 C F R. 1 51) | INTERNATIONAL APPLICATION NO | ATTORNEY'S DOCKET NUMBER |
|---|---|---|
| 10/088192 | PCT/US00/25156 | 0887-4149US2 |

**21.** ☒ The following fees are submitted:

**BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5) ):**

| | CALCULATIONS PTO USE ONLY | |
|---|---|---|

Neither international preliminary examination fee (37 CFR 1.482)
nor international search fee (37 CFR 1.445(a)(2) paid to USPTO
and International Search Report not prepared by the EPO or JPO _____ $1040.00

International preliminary examination fee (37 CFR 1.482) not paid to
USPTO but International Search Report prepared by the EPO or JPO _____ $890.00

International preliminary examination fee (37 CFR 1.482) not paid to
USPTO but international search fee (37 CFR 1.445(a)(2) paid to USPTO __ $740.00

International preliminary examination fee paid to USPTO (37 CFR 1.482)
but all claims did not satisfy provisions of PCT Article 33 (1) - (4) _____ $690.00

International preliminary examination fee paid to USPTO (37 CFR 1.482)
and all claims satisfied provisions of PCT Article 33(1) - (4) _____ $100.00

| ENTER APPROPRIATE BASIC FEE AMOUNT = | $100.00 | |
|---|---|---|

Surcharge of **$130** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).

| CLAIMS | NUMBER FILED | NUMBER EXTRA | RATE | | |
|---|---|---|---|---|---|
| Total claims | 16 - 20 = | 0 | X $18.00 | $0.00 | |
| Independent claims | 2 - 3 = | 0 | X $84.00 | $0.00 | |
| MULTIPLE DEPENDENT CLAIM(S) (if applicable) | | | + $280.00 | $0.00 | |
| **TOTAL OF ABOVE CALCULATIONS =** | | | | $100.00 | |
| ☒ Applicant claims small entity status. See 37 C.F.R. 1.27. The fees indicated above are reduced by 1/2. | | | | $50.00 | |
| **SUBTOTAL =** | | | | $50.00 | |
| Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)). | | | | $0.00 | |
| **TOTAL NATIONAL FEE =** | | | | $50.00 | |
| Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property X = | | | | $0.00 | |
| **TOTAL FEES ENCLOSED =** | | | | $50.00 | |
| | | | | Amount to be refunded: | $ |
| | | | | charged: | $ |

a. ☒ A check in the amount of $50.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 13-4500, ORDER NO. _____ in the amount of $0.00 to cover the above fees.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 13-4500, ORDER NO. 0887-4149US2. A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

**NOTE:** Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

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# IMAGING OF SCATTERING MEDIA
## USING RELATIVE DETECTOR VALUES

This invention was made with U.S. Government support under contract number

5   CA-RO166184-02A, awarded by the National Cancer Institute. The U.S. Government

has certain rights in the invention.

This application claims the benefit under 35 U.S.C. §120 of prior U.S. Provisional

Patent Application Serial Nos. 60/153,769 filed September 14, 1999, entitled

TOMOGRAPHY IN A SCATTERING MEDIUM, 60/153,926 filed September 14, 1999,

10   entitled DYNAMIC TOMOGRAPHY IN A SCATTERING MEDIUM and 60/154,099

filed September 15, 1999, entitled DYNAMIC TOMOGRAPHY IN A SCATTERING

MEDIUM.

This application is related to copending application serial number "not yet

assigned", attorney docket number 0887-4147PC1, filed on the same date as this

15   application, entitled "SYSTEM AND METHOD FOR TOMOGRAPHIC IMAGING OF

DYNAMIC PROPERTIES OF A SCATTERING MEDIUM" by inventors R. Barbour

and C. Schmitz and is hereby incorporated by reference (hereinafter the "Barbour

4147PC1 application")

This application is also related to copending application serial number "not yet

20   assigned", attorney docket number 0887-4149PC1, filed on the same date as this

application, entitled "METHOD AND SYSTEM FOR IMAGING THE DYNAMICS OF

A SCATTERING MEDIUM" by inventor R. Barbour and is hereby incorporated by

reference (hereinafter the "Barbour 4147PC2 application").

**Field of the Invention**

The invention relates generally to imaging in a scattering medium, and more particularly, to a method using a novel modification to the perturbation formulation of the radiation transport inverse problem to determine relative changes in the absorption and/or scattering properties of the medium based on relative changes in measured energy.

5    **Background of the Invention**

Many techniques and systems have been developed to image the interior structure of a turbid medium through the measurement of energy that becomes scattered upon being introduced into a medium. Typically, a system for imaging based on scattered energy detection includes a source for directing energy into a target medium and a

10   plurality of detectors for measuring the intensity of the scattered energy exiting the target medium at various locations with respect to the source. Based on the measured intensity of the energy exiting the target medium, it is possible to reconstruct an image representing the cross-sectional scattering and/or absorption properties of the target. Exemplary methods and systems are disclosed in Barbour et al., U.S. Patent No.

15   5,137,355, entitled "Method of Imaging a Random Medium," (hereinafter the "Barbour '355 patent"), Barbour, U.S. Patent No. 6,081,322, entitled "NIR Clinical Opti-Scan System," (hereinafter the "Barbour '322 patent"), the Barbour 4147PC1 application, and the Barbour 4147PC2 application.

Imaging techniques based on the detection of scattered energy are capable of

20   measuring the internal absorption, scattering and other properties of a medium using sources whose penetrating energy is highly scattered by the medium. Accordingly, these techniques permit the use of wavelengths and types of energy not suitable for familiar transmission imaging techniques. Thus they have great potential for detecting properties

2

of media that are not accessible to traditional energy sources used for transmission

imaging techniques. For example, one flourishing application of imaging in scattering

media is in the field of optical tomography. Optical tomography permits the use of near

infrared energy as an imaging source. Near infrared energy is highly scattered by human

5    tissue and is therefore an unsuitable source for transmission imaging in human tissue.

However, these properties make it a superior imaging source for scattering imaging

techniques. The ability to use near infrared energy as an imaging source is of particular

interest in clinical medicine because it is exceptionally responsive to blood volume and

blood oxygenation levels, thus having great potential for detecting cardiovascular disease,

10   tumors and other disease states.

A common approach for the reconstruction of an image of the cross-sectional

properties of a scattering medium is to solve a perturbation equation based on the

radiation transport equation. The radiation transport equation is a mathematical

expression describing the propagation of energy through a scattering medium. The

15   perturbation formulation relates the difference between coefficient values of the true

target and a specified reference medium, weighted by a proportionality coefficient whose

value depends on, among other things, the source/detector configuration and the optical

properties of the medium. In practice, tomographic measurements consider some array of

measurement data, thus forming a system of linear equations having the form

20
$$\mathbf{u} - \mathbf{u}_r = \delta\mathbf{u} = \mathbf{W}_r\delta\mathbf{x}, \tag{1}$$

where $\delta\mathbf{u}$ is the vector of differences between a set of measured light intensities ($\mathbf{u}$) and those

predicted for a selected reference medium ($\mathbf{u}_r$), $\mathbf{W}_r$ is the Jacobian operator, and $\delta\mathbf{x}$ is the

position–dependent difference between one or more optical properties of the target and reference

media (*i.e.*, a change in absorption coefficient $\delta\mu_a$, a change in the reduced scattering coefficient,

$\mu'_s$, or, in the diffusion approximation, the diffusion coefficient $\delta D$, where $D = 1/[3(\mu_a + \mu'_s)]$). The operator, referred to as the weight matrix, has coefficient values that physically represent the fractional change in light intensity at the surface caused by an incremental change in the optical properties at a specified point in the medium. Mathematically this is represented by the partial differential operator $\partial u_i/\partial x_j$, where $i$ is related to the $i^{th}$ source/detector pairs at the surface of the medium, and $j$ to the $j^{th}$ pixel or element in the medium.

Although the perturbation equation in Eq. (1) can be solved using any of a number of available inversion schemes, practical experience has shown that the accuracy and reliability of the results obtained can vary greatly due to uncertainties and errors associated with the quality of the measurement data, inaccuracies in the physical model describing light propagation in tissue, specification of an insufficiently accurate reference state, the existence of an inherently underdetermined state caused by insufficiently dense measurement sets, weak spatial gradients in the weight function, and so forth.

In practice, a matter of considerable concern is the accuracy with which the reference medium can be chosen. An accurate reference is one that closely matches the external geometry of the target medium, has the same size, nearly the same internal composition, and for which the locations of the measuring probes and their efficiency coincide well with those used in the actual measurements. While such conditions may be easily met in numerical and perhaps laboratory phantom studies, they represent a much greater challenge in the case of tissue studies. Confounding factors include the plasticity of tissue (it deforms upon probe contact), its mainly arbitrary external geometry and internal composition and the considerable uncertainty stemming from the expected variable coupling efficiency of light at the tissue surface. The influence of these uncertainties can be appreciated when it is recognized that the input data vector for the standard perturbation formulation (*i.e.*, Eq. (1)) is actually the <u>difference</u> between a measured and a computed quantity. This vector contains information regarding the subsurface properties of the

4

target medium that, in principle, can be extracted <u>provided</u> an accurate reference medium is available.

In practice, however, there are two significant concerns that are frequently encountered in experimental studies and are not easily resolvable especially in the case of tissue studies. One concern is the expected variable coupling efficiency of light entering and exiting tissue. Nonuniformity in the tissue surface, the presence of hair or other blemishes, its variable deformation upon contact with optical fibers, the expected variable reactivity of the vasculature in the vicinity of the measuring probe all serve to limit the ability to accurately determine the in-coupling and out-coupling efficiencies of the penetrating energy. Consideration of this issue is critical as variations in the coupling efficiency will be interpreted by the reconstruction methods as variations in properties of the target medium and can introduce gross distortions in the recovered images. In principle, the noted concern can be minimized by adopting absolute calibration schemes, however, in practice the variability in tissue surface qualities will limit reliability and stability of these efforts.

A second concern stems from the underlying physics of energy transport in highly scattering media. One effect of scattering is to greatly increase the pathlength of the propagating energy. Small changes in the estimated absorption or scattering properties of the medium can, depending on the distance separating the source and detector, greatly influence the density of emerging energy. This consideration has important implications regarding the required accuracy by which the reference medium must be specified. In the context of perturbation formulations, the reference medium serves to provide estimates of the predicted energy density as well as to provide the needed weight functions that serve as the imaging operators. The difficulty is that the computed reference intensity values are extremely dependent on the optical coefficient values of the reference medium. Significantly, this dependence is a nonlinear function of the distance between source and detector. It follows that a small change in the optical properties of the reference medium may influence the value of the computed intensity differences $(\delta u)$ by a

relative amount that may be significantly different for each source/detector pair, thereby altering

the information content of the data vectors. This can lead to the recovery of grossly corrupted

images. Whereas, in principle, such effects may be overcome by use of recursive solutions to the

perturbation equation (i.e., Newton-type updates), in practice this can require extensive

5    computational efforts, especially in the case of 3D solutions. Moreover, it is well appreciated that

such efforts to improve on first order solutions to the perturbation equation (e.g., Born or Rytov

solutions), can fail if the initial estimate chosen for the reference medium is insufficiently

accurate.

One alternative to devising absolute calibration schemes is to devise

10   methodologies whose solutions are intrinsically less sensitive, or better still, do not

require such information, but nevertheless are capable of providing accurate descriptions

of certain features of highly scattering media. While a range of empirical methodologies

can be devised, it is desirable that they be broadly extendable without requiring undue

physical approximations, since these are generally incompatible with model-based

15   methods.

An approach previously adopted is to directly relate relative detector readings,

obtained from comparison of detector values derived from two different target media

(usually media with and without the included object), to the weight matrix computed

based on a previously assigned reference medium. R. L. Barbour, H. Graber, R. Aronson,

20   and J. Lubowsky, "Model for 3-D optical imaging of tissue," Int. Geosci. and Remote

Sensing Symp., (IGARSS), 2, 1395-1399 (1990). While capable of producing good

quality images of internal structure of a target medium, the method proved to have

limited utility as it did not produce solutions having physical units, thereby rendering

specific interpretation difficult, as well as limiting efforts to compute recursive solutions.

For the forgoing reasons, there is a need for image reconstruction techniques based on the detection of scattered energy that (1) do not require absolute calibration of, and absolute measurements by, the detectors and other elements of the apparatus, (2) make the standard perturbation equation less susceptible to variations between boundary conditions and properties of the reference medium and the target medium, and (3) produce solutions having physical units.

## SUMMARY

The present invention satisfies these needs by providing a method for generating an image of a scattering medium using normalized relative measured intensity values a perturbation formulation based on the radiation transport equation.

It is an object of the present invention to provide a method for imaging the properties of a scattering target medium using a modified perturbation equation. The method comprises generating a first data vector of measured data from a target and a second vector of measured data from a target, normalizing the first and second vectors of measured data and solving a modified perturbation equation for the unknown optical properties of a target medium. The first and second vectors of measured data are measures of energy emerging from the target.

It is a further aspect of this invention to obtain the first and second sets of measured data from the same target, wherein the first set of measured data is a set of data measured at an instant in time and the second set of measured data is a time average mean of a plurality of first sets of measured data.

It is yet a further aspect of this invention to obtain the first and second sets of measured data from two different targets.

In another aspect of this invention the modified perturbation equation is a

modified Rytov approximation.

In another aspect of this invention the modified perturbation equation is a modified Born

approximation.

5                              **BRIEF DESCRIPTION OF THE FIGURES**

For a better understanding of the invention, together with the various features and

advantages thereof, reference should be made to the following detailed description of the

preferred embodiment and to the accompanying drawings, wherein:

FIG. 1 is a schematic illustration of an exemplary imaging system;

10          FIG. 2A is a cross-sectional image of the absorption coefficients of the target;

FIG. 2B is a cross-sectional image of the diffusion coefficients of the target;

FIG. 3 is a table illustrating a summary of the test cases explored;

FIG. 4A is a series of reconstructed cross-sectional absorption profile images of

the target obtained in test case 1 of FIG. 3;

15          FIG. 4B is a series of reconstructed cross-sectional diffusion profile images of the

target obtained in test case 1 of FIG. 3;

FIG. 5A is a series of reconstructed cross-sectional absorption profile images of

the target obtained in test case 2 of FIG. 3;

FIG. 5B is a series of reconstructed cross-sectional diffusion profile images of the

20    target obtained in test case 2 of FIG. 3;

FIG. 6A is a series of reconstructed cross-sectional absorption profile images of

the target obtained in test case 3 of FIG. 3;

FIG. 6B is a series of reconstructed cross-sectional diffusion profile images of the target obtained in test case 3 of FIG. 3;

FIG. 7A is a series of reconstructed cross-sectional absorption profile images of the target obtained in test case 5 of FIG. 3;

5       FIG. 7B is a series of reconstructed cross-sectional diffusion profile images of the target obtained in test case 5 of FIG. 3;

FIG. 8A is a series of reconstructed cross-sectional absorption profile images of the target obtained in test case 6 of FIG. 3;

FIG. 8B is a series of reconstructed cross-sectional diffusion profile images of the target obtained in test case 6 of FIG. 3;

FIG. 9A is a series of reconstructed cross-sectional absorption profile images of the target obtained in test case 7 of FIG. 3;

FIG. 9B is a series of reconstructed cross-sectional diffusion profile images of the target obtained in test case 7 of FIG. 3;

FIG. 10 is a table listing constant calibration errors corresponding to each image of FIGS. 9A and 9B;

FIG. 11 is a table of data corresponding to the error, resolution and contrast for the reconstructed images shown in FIGS. 4A and B;

FIG. 12 is a table of data corresponding to the error, resolution and contrast for
20      the reconstructed images shown in FIGS. 5A and B;

FIG. 13A is a series of reconstructed cross-sectional absorption profile images of the target shown in FIG. 15 with varying concentrations of hemoglobin;

9

FIG. 13B is a series of reconstructed cross-sectional diffusion profile images of the target shown in FIG. 15 with varying concentrations of hemoglobin;

FIG. 14A is a series of reconstructed cross-sectional absorption profile images of the target shown in FIG. 15 with varying reference medium properties;

5       FIG. 14B is a series of reconstructed cross-sectional diffusion profile images of the target shown in FIG. 15 with varying reference medium properties;

FIG. 15 is a schematic illustration of a phantom study;

FIG. 16A is a graph plotting the amplitude of normalized intensities used in the modified perturbation formulation corresponding to the reconstructed cross-sectional

10      images shown in row 3 of FIG. 4;

FIG. 16B is a graph plotting the amplitude of normalized intensities used in the modified perturbation formulation corresponding to the reconstructed cross-sectional images shown in column 3 of FIG. 4;

FIG. 17A is a graph plotting the amplitude of the relative intensities used in the

15      standard perturbation formulation corresponding to the reconstructed cross-sectional images shown in row 3 of FIG. 5;

FIG. 17B is a graph plotting the amplitude of the relative intensities used in the standard perturbation formulation corresponding to the reconstructed cross-sectional images shown in column 3 of FIG. 5;

20      FIG. 18 is a graph plotting the amplitude of the frequency spectrum of the Fourier transforms for data vectors computed using equation (1) and equation (3); and

FIG. 19 is a table illustrating the ratio of average contrasts of reconstructed absorption and diffusion coefficients shown in FIGS. 4A and B respectively.

## DETAILED DESCRIPTION OF THE INVENTION

Imaging in a scattering medium relates to the methods and techniques of image the internal properties of a medium based on the detection of scattered energy. The typical process for imaging of a scattering medium comprises: (1) selecting a

5    reference medium having known boundary conditions and optical properties which are substantially similar to those of the intended target; (2) determining a weight matrix and an intensity of emerging energy exiting the reference medium at each of a plurality of source points for each of a plurality of detectors located around the reference medium boundary, the determination being made by either actual measurements or solution of the

10   radiation transport equation; (3) measuring actual emerging energy intensities for corresponding source and detector points on a target medium; and (4) solving the perturbation equation for the optical properties of the target based on the measured intensities of energy emerging from the target.

The present invention describes an improved methodology for imaging of a

15   scattering medium using a modified form of the standard perturbation equation. The inventive modification of the standard perturbation equation is capable of (1) reducing the sensitivity of the perturbation equation to differences between the reference medium and target medium, (2) producing solutions to the perturbation equation having physical units, and (3) reducing the effect of variable detector efficiencies without the need for

20   absolute calibration, while at the same time preserving the ability to compute recursive solutions. Compared to the standard perturbation approach, the described invention provides remarkable improvement in the quality of image reconstruction.

11

While the method of the present invention is applicable to known static imaging techniques it is instrumental in the realization of practical dynamic imaging of highly scattering media. There are three principal elements to practical dynamic imaging. The first element is the development of a fast, parallel, multi-channel acquisition system that

5    employs geometrically adaptive measuring heads. This system is described briefly below and in further detail in the copending Barbour 4147PC1 application. The second element is to evaluate the acquired tomographic data using the modified perturbation methods of the present invention. The third element is to collect a time series of data and subject either the time series of data or a time series of reconstructed images from the data to

10   analysis using various linear and nonlinear time-series analysis methods to extract dynamic information and isolated dynamic information. These methods are described in detail in the copending Barbour 4147PC2 application.

Some of the methods, systems and experimental results described below focus on optical tomography of human tissue using wavelengths in the near infrared region for the

15   imaging source. However, as disclosed generally herein, it will be appreciated to those skilled in the art that the invention is applicable to the use of essentially any energy source (e.g., electromagnetic, acoustic, and the like) on any scattering medium (e.g., body tissues, oceans, foggy atmospheres, earth strata, industrial materials) so long as diffusive type mechanisms are the principal means for energy transport through the medium.

20   **System**

Numerous imaging systems such as those disclosed in the previously mentioned the Barbour '355 patent, the Barbour '322 patent and the Barbour 4147PC1 application have been developed for use in imaging of a scattering medium. A schematic illustration

of an exemplary system is shown in FIG. 1. This system includes a computer 102, sources 104, 106, a source demultiplexer 108, an imaging head 110, detectors 112 and a data acquisition board 114.

5      A target 116 placed in the imaging head 110 is exposed to optical energy from sources 104, 106. The optical energy originating from sources 104, 106, is combined by beam splitter 118 and is delivered to source demultiplexer 108. The source demultiplexer 108 is controlled by computer 102 to direct the optical energy to source fibers 120 sequentially.

Each source fiber 120 carries the optical energy from the demultiplexer 108 to the

10      imaging head 110, where the optical energy is directed into the target 116. The imaging head 110 contains a plurality of source fibers 120 and detector fibers 122 for transmitting and receiving light energy, respectively. Each source fiber 120 forms a source-detector pair with each detector fiber 122 in the imaging head 110 to create a plurality of source-detector pairs. The optical energy entering the target 116 at one location is scattered and

15      may emerge at any location around the target 116. The emerging optical energy is collected by detector fibers 122 mounted in the imaging head 110.

The detector fibers 122 carry the emerging energy to detectors 112, such as photodiodes or a CCD array, that measure the intensity of the optical energy and deliver a corresponding signal to a data acquisition board 114. The data acquisition board 114, in

20      turn, delivers the data to computer 102.

This imaging process is repeated so as to deliver optical energy to each of the source fibers sequentially, a measurement being obtained for detected emerging energy at each detector for each emitting source fiber. This process may continue over a period of

time with the computer 102 storing the data for reconstruction of one or more images.

Additionally, the system may include two or more imaging heads for comparing one

target to another.  The computer 102 reconstructs an image representative of the internal

optical properties of the target by solving a perturbation equation.  It will be appreciated

5    by those skilled in the art that more than one computer can be used to increase data

handling and image processing speeds.

**The Standard Perturbation Formulation**

As discussed above, reconstruction of a cross section image of the absorption

and/or scattering properties of the target medium is based on the solution of a

10   perturbation formulation of the radiation transport equation.  The perturbation method

assumes that the composition of the unknown target medium deviates only by a small

amount from a known reference medium.  This reduces a highly non-linear problem to

one that is linear with respect to the difference in absorption and scattering properties

between the target medium under investigation and the reference medium.  The resulting

15   standard perturbation equation has the following forms:

$$\mathbf{u} - \mathbf{u}_r = \delta\mathbf{u} = \mathbf{W}_r\delta\mathbf{x},\qquad\qquad(1)$$

In equation (1), $\delta\mathbf{u}$ is a vector of source-detector pair intensity differences between the

measured target medium and the known reference medium (i.e., $\delta\mathbf{u} = \mathbf{u} - \mathbf{u}_r$).  W is the

weight matrix describing the influence that each volume element ("voxel") of the

20   reference medium has on energy traveling from each source to each detector, for all

source-detector pairs.  The volume elements are formed by dividing a slice of the

reference medium into an imaginary grid of contiguous, non-overlapping pieces.

Physically, the weight matrix contains the first order partial derivatives of the detector

14

responses with respect to the optical coefficients of each volume element of the reference medium. $\delta x$ is the vector of differences between the known optical properties (e.g., absorption and scattering coefficients) of each volume element of the reference medium and the corresponding unknown optical properties of each volume element of the target

5    medium.

This standard perturbation equation assumes (1) use of absolute detector measurements for $u$, and (2) that the boundary conditions and optical properties of the reference do not vary significantly from the target. Both of these factors are problematic in practice.

10   **The Modified Perturbation Formulation**

The present invention modifies the standard perturbation equation by replacing $\delta u$ with a proportionate relative difference between two measured values multiplied by a reference term of the required units as set forth in the equation (2) below:

$$\left(\delta I_r\right)_i = \left[\frac{I_i - (I_0)_i}{(I_0)_i}\right](I_r)_i \qquad (2)$$

15   where $i$ is the source/detector pair index. In equation (2), $I_r$ is the computed detector reading corresponding to a source-detector pair of a selected reference medium, and $I$ and $I_0$ represent two data measurements for a corresponding source-detector pair on one or more targets (e.g., background vs. target, or time-averaged mean vs. a specific time point, etc.). The resultant term $\delta I_r$ therefore represents a relative difference between two sets of

20   measured data that is then mapped onto a reference medium. Careful examination reveals that this modification has important attributes that limit the effects of modeling

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errors and minimize ill-conditioning of the inverse problem while retaining the correct

units in the solution.

The corresponding perturbation equation using this modified term is:

$$\mathbf{W}_r \cdot \delta \mathbf{x} = \delta \mathbf{I}_r \qquad (3)$$

5   In equation (3) $\mathbf{W}_r$ and $\delta \mathbf{x}$ are the same as $\mathbf{W}_r$ and $\delta \mathbf{u}$ in equation (1). Referring to

equations (2) and (3), it can be seen that in the limit, when $I_r$ equals to $I_0$, this equation

reduces to the standard perturbation formulation shown in equation (1). This formulation

represents the Born approximation formulation of the modified perturbation equation. A

similar expression may be written for the Rytov approximation in the following form:

$$\left(\delta \mathbf{I}'\right)_i = \ln \frac{I_i}{\left(\mathbf{I}_o\right)_i};$$

$$\left(\mathbf{W}_r'\right)_{ij} = \frac{\left(\mathbf{W}_r\right)_{ij}}{\left(\mathbf{I}_r\right)_i}; \qquad (4)$$

$$\delta \mathbf{I}' = \mathbf{W}_r' \delta \mathbf{x}$$

The inventive operation accomplished by equation (2) is to preserve the information

content of a measured proportionate relative data vectors obtained from the target

medium and to yield data vectors having the correct physical units.    Apart from

simplifying measurement requirements, the method represented by equations (3) and (4)

15   also reduces susceptibility of the perturbation equation to boundary and optical property

variation between the target and the reference medium. Additionally, iterative solutions

of equations (3) and (4) can be easily implemented. In principle, the techniques used in

the modified perturbation equation, referred to as the normalized difference method

(NDM), can be used to evaluate any measured proportionate relative quantity.

## Experimental Validation

The following discussion presents results validating the methods and advantages of the present inventions. These examples are presented merely as an illustration of the benefits of applying the NDM approach for the analysis of relative measures from highly

5 scattering media.

## Forward Model and Data Acquisition Geometry

For any intended target the perturbation equation is generated for a reference medium having boundary conditions and optical properties substantially similar to the target. The perturbation equation models the energy propagation, e.g. light, in the

10 reference medium as a diffusion process. For a domain $\Omega$ having a boundary $\partial\Omega$, this is represented by the expression:

$$\nabla \cdot \left[ D(\mathbf{r}) \nabla u(\mathbf{r}) \right] - \mu_a(\mathbf{r}) u(\mathbf{r}) = \delta(\mathbf{r} - \mathbf{r}_s), \qquad \mathbf{r} \in \Omega \qquad (5)$$

where u(r) is the photon density at position r, $r_s$ is the position of a DC point source, and D(r) and $\mu_a$(r) are the position-dependent diffusion and absorption coefficients,

15 respectively. The diffusion coefficient is defined as:

$$D = 1 / \left[ 3 \left( \mu_a[\mathbf{r}] + \mu_s'[\mathbf{r}] \right) \right] \qquad (6)$$

where $\mu_s'[\mathbf{r}]$ is the reduced scattering coefficient. The photon density values at the detectors, i.e., the calculated energy intensity emerging from the reference medium at each detector, were computed by applying Dirichlet boundary conditions on an

20 extrapolated boundary. Depending on the target medium to be explored, sources and detectors for the reference are positioned 1 to 2 transport mean free pathlengths within the boundary of the reference medium.

Solutions to the diffusion equation may be computed by any known means, such as by the KASKADE adaptive finite element method. R. Beck, R. Erdmann and R. Roitzsch, "Kaskade 3.0 – An object-oriented adaptive finite element code," Technical report TR 95-4, Konrad-Zuse-Zentrum fur Informationstechnik, Berlin (1995). This is a publicly available code suitable for the solution of partial differential equations in one, two or three dimensions using adaptive finite element techniques. The code can be readily modified to permit solutions to the diffusion equation using a point source. Mesh generation may be by any known method, such as the Delaunay tessellation algorithm originally proposed by Watson. D. F. Watson, "Computing the n-dimensional Delaunay tessellation with applications to Voronoi polytopes", Computer Journal, 24, 167-172 (1981).

The perturbation equation is specific to the boundary conditions and optical properties of the reference medium, including the orientation of the source-detector pairs in relation to one another and the reference medium. These conditions and properties are preferably nearly identical to the target. For example, in the experiments discussed below, the perturbation equation was generated based on an imaging system having six sources and eighteen detectors per source (108 source-detector pairs) with the sources equally spaced at 60 degree intervals around the boundary of the medium and the detectors equally spaced at 20 degree intervals.

**Inverse Algorithm**

As described above, in the present invention relative intensities are measured for all source-detector pairs using any known imaging system. Image recovery is then achieved using known methods, such as conjugate gradient descent (CGD), or

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simultaneous algebraic reconstruction techniques (SART), to solve the modified

perturbation equation for the absorption and scattering properties of the target. J. Chang,

H. L. Graber, R. L. Barbour and R. Aronson, "Recovery of optical cross-section

perturbations in dense-scattering media by transport-theory-based imaging operators and

5    steady-state simulate data", Appl. Opt. 35, 3963-3978, (1996) (the disclosure of which is

incorporated herein by reference).  For example, the experimental results discussed below

were achieved using a CGD solver with and without matrix rescaling.  In addition, a

weight matrix rescaling (WMR) technique may be used to improve the ill-conditioning of

the weight matrix.  The effect of rescaling the weight matrix is to make it more uniform.

10   Two rescaling criteria can be applied for this purpose: (1) rescaling the maximum of each

column to 1; or (2) rescaling the average of each column to 1.  In the experimental results

below, when WMR was used, criterion 1 was applied for image recovery.

The solution to the modified perturbation equation provides a relative measure of the

difference between the cross-sectional optical properties of a target during the first and

15   second measurements I and $I_0$.  The values from this solution are used to generate cross-

sectional images representative of the target's internal optical properties.

**Test Cases Explored**

        The following discussion presents results obtained for seven test cases comparing

image reconstruction using the known standard perturbation formulation with the

20   modified perturbation formulation of the present invention.  These examples are

presented merely as an illustration of the benefits of the modified perturbation method of

the present invention.

The reconstruction results presented in the test case are limited to solution of the

first order Born approximation. The coefficient values for absorption and diffusion

coefficients were computed simultaneously. For each case tested, measures of error,

contrast accuracy and resolution were also computed. These are defined as follows:

5          i.          Image error is the relative root mean square error (RMSE)

$$RMSE = \sqrt{\frac{\sum_{j=1}^{M}(x_j - a_j)^2}{\sum_{j=1}^{M}(a_j)^2}} \qquad (7)$$

where $a_j$ and $x_j$ are the actual and reconstructed values of the optical coefficient, and M is

the number of volume elements used for reconstruction.

           ii.         Image contrast accuracy was determined by computing the mean value of

10    the recovered perturbation coefficient along the transect bisecting the two objects.

           iii.        Resolution was measured by computing the mean value of the full-width

half-maximum of the two reconstructed objects along the transect bisecting the

inclusions.

           FIGS. 2A and 2B show the cross-sectional geometry and absorption (FIG. 2A)

15    and diffusion (FIG. 2B) coefficient profiles of the target medium explored. The target

medium is 8cm in diameter and has two included objects each 1 cm in diameter and

separated by 3 cm symmetrically about the center of a homogeneous background

medium. Optical properties of the background and included objects are 0.04 and 0.02

cm$^{-1}$ for $\mu_a$ (absorption coefficient), and 10 and 5 cm$^{-1}$ for $\mu_s$ (scattering coefficient),

20    respectively.

The table of FIG. 3 lists the various test cases explored. The symbol "V" indicates that the parameter was varied, "C" indicates that the parameter was held constant, and "/" indicates that the parameter was not considered. The test cases allowed at least partial isolation of the effect of variations in each of the input parameters on the

5 resultant image for different reconstruction schemes and perturbation formulations. This testing permitted exploration of the dependence of ill-conditioning on the different input parameters that influence the accuracy and stability of the image reconstruction.

Test cases 1 and 2 examined the general case where the reference medium is based only on an estimate of the background optical properties of the target medium. The

10 estimated properties were varied over a broad range, ranging from 0.0 $\text{cm}^{-1}$ to 0.3 $\text{cm}^{-1}$ in $\mu_a$, and from 3 $\text{cm}^{-1}$ to 30 $\text{cm}^{-1}$ in $\mu_s$. For purposes of comparison, test cases 3 through 7 explored the dependence of image quality on the varied parameters using the standard perturbation formulation.

Test cases 3 and 4 mainly mirror conditions explored in cases 1 and 2 with the

15 exceptions that the standard perturbation formulation was evaluated, and a narrower range of coefficient values was considered for the reference medium. Here the general case is also considered where only an estimate of the background optical properties of the target medium is available. The range of values for the optical properties explored were from 0.02 $\text{cm}^{-1}$ to 0.08 $\text{cm}^{-1}$ in $\mu_a$, and from 5 $\text{cm}^{-1}$ to 15 $\text{cm}^{-1}$ in $\mu_s$.

20 Cases 5 and 6 consider the special situation where prior knowledge of the background properties of the target medium is known. The parameters varied were $W_r$ and $I_r$, referred to as $W_b$ and $I_b$, respectively. The range of optical properties varied for test 5 is same as in case 1. For case 6, the range of optical properties varied is the same

as in case 3. Test case 7 explores the effect of a constant calibration error in

measurement, and assumes prior knowledge of the background properties of the target

medium.

**Results**

5          Data shown in FIGS. 4 through 9 illustrates the influence that the varied

parameters listed in FIG. 3 have on the reconstruction results derived from a first-order

Born approximation using the standard and modified perturbation formulations. The

results presented are listed in a matrix format. The value of the absorption and scattering

coefficient for the reference medium is fixed for each row and column, respectively.

10    Varied is the value of these parameters along the orthogonal direction. Shown in the

figures are the reconstruction profiles for all test cases explored except case 4, whose

findings are reported in the text.

**Qualitative Analysis**

          Data in FIGS. 4 and 5 show the quality of reconstructed images obtained using

15    equation (3). FIGS. 4A and 5A illustrate the computed absorption maps, while FIGS. 4B

and 5B show the computed diffusion maps. Compared to the original profiles shown in

FIG. 2, these findings illustrate that qualitatively accurate results, revealing the two-

object structure, are obtained over a broad range of values for the selected reference

medium. Artifact dominated results are limited to cases in the lower right corner of the

20    matrix. These correspond to those reference media having absorption and scattering

coefficient values significantly greater than the background of the target medium.

Quantitative analysis of these results is presented in the next section. Comparison of

images shown in FIGS. 4 and 5 reveals that the matrix rescaling method is capable of

providing a higher resolution image, though over a reduced range of values for the

reference medium. For example, comparison of results reveals that the matrix rescaling

method yields only artifacts in the absorption map for non-absorbing reference media,

while under the same conditions the diffusion coefficient maps reveal two completely

5      resolved objects. In the absence of matrix rescaling, both coefficient maps reveal the

presence of the included objects, though with reduced edge resolution and more artifacts

in the diffusion map. The added improvement using matrix rescaling, however, is

achieved under the limiting conditions of a range constraint (positive for D and negative

for $\mu_a$). Overall, the range of values for the reference medium's optical properties for

10     which qualitatively accurate maps are obtained for both inverse methods is much greater

than previously reported. S. R. Arridge, M. Schweiger, "Sensitivity to prior knowledge

in optical tomographic reconstruction", in Proc. Optical tomography, photon migration

and spectroscopy of tissue and model media: Theory, human studies, and

instrumentation, SPIE, 2389, 378-388, (1995) (the disclosure of which is incorporated

15     herein by reference).

Shown in FIG. 6 are results from case 3 evaluated using equation (1). Compared

to results shown in FIGS. 4 and 5, a more limited range of values of optical properties for

the reference medium were examined, since outside of this range, only artifact was

recovered. Even within the explored range, significant instability was observed for

20     relatively small variations in the reference medium. This sensitivity indicates a state of

ill-conditioning that is alleviated using the modified perturbation formulation (equation

3). Not shown are results from case 4 using the matrix rescaling method. In case 4, even

greater instability was observed than in the case using CGD only.

The parameters varied in the above figures include both the computed reference intensity and the weight matrix. This is the general case where both quantities can only be estimated and are computed from a specified reference medium.

Results shown in FIGS. 7 through 9 explore the special cases where errors occur only in one parameter. Data in FIG. 7 illustrates the influence of errors in the estimated weight matrix. Assumed is prior knowledge of the reference detector intensity values for the background medium. In practice this would correspond to situations where a measurement was made in the presence and absence of an included object. Inspection reveals that qualitatively accurate results are obtained over a significantly broader range of reference values than those presented in FIG. 7. This finding suggests that the principal origin of the ill-conditioning of the inverse problem is associated with errors in the estimated reference intensity.

Results shown in FIG. 8 explore this possibility directly. In this situation, we assume the unlikely case where accurate prior knowledge of the weight matrix for the target medium is available. Comparison of the results in FIG. 8 to the results in FIG. 6 illustrates some improvement in the range of reference media yielding qualitatively accurate results. However, this range is small compared to the situations tested in FIG. 8 for the standard perturbation formulation and for the modified perturbation formulation in FIGS. 4 and 5.

Finally, in FIG. 9, we test the case where accurate prior knowledge for the weight matrix and reference detector values are available and a constant error of measurement is introduced. The error added to the measured detector reading, I, varies from −50 to 900%. Variations in constant calibration error corresponding to FIG. 8 are shown in FIG.

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9. Under these conditions, the results show that a constant calibration error does not significantly affect the qualitative accuracy of the computed images. It is worth noting that errors of this type will not exist using the modified perturbation formulation.

**Quantitative Analysis**

5    A quantitative analysis of the image data was made by computing measures of error, resolution and contrast. Results shown in FIGS. 11 and 12 are the corresponding values computed from data shown in FIGS. 4 and 5. The format of the data is the same as in FIG. 4 (i.e.,, data in the rows are derived for a fixed value of absorption, while column data is derived for a fixed value of scattering).

10    Inspection of FIGS. 11 and 12 reveals, not surprisingly, that the lowest image RMSE is achieved when the selected reference medium matches the background optical properties of the target medium. Consistent with this finding is that nearly equivalent error values were obtained for those maps in which one of the fixed coefficient values for the reference medium matched that of the background. Interestingly, in the absence of

15    WMR, whereas these conditions produced the lowest total error values for the image map, improved accuracy of object contrast was obtained using reference media generally having reduced scattering and increased absorption values compared to those of the background. An exception to this was the case where the background absorption level in the reference medium was reduced while scattering value matched the object. With

20    WMR, the best accuracy for object coefficient values was achieved when the reference medium matched the coefficient values of the background medium. This is not unexpected given the imposed constraint. Overall there is evidence of a trade-off between artifact levels and accuracy in object contrast. Potentially significant is the

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observation of several instances where considerably enhanced object contrast is seen

without undue degradation of image quality. This is observed with either inverse

algorithm, though the trends are somewhat different. In the absence of WMR, enhanced

contrast for both absorption and diffusion maps are seen using reference media whose

5      absorption and scattering coefficient values are lower than the background. Enhanced

contrast is also seen in the case of a non-absorbing reference medium, although increased

artifacts are present. With WMR, improved object contrast is also seen with reference

media having reduced scattering, but the trend in contrast enhancement is opposite for the

different coefficients and depends strongly on the value of the absorption coefficient.

10     Increasing the absorption coefficient value for the reference medium increases the object

contrast value for absorption while reducing the contrast for the diffusion coefficient.

Inspection of results reported for edge resolution reveal an under and over estimate of

object diameter for images computed with and without the WMR, respectively. Whereas

it is often best to avoid errors in edge resolution, the resolution of the images obtained

15     using the WMR method is striking.

**Experimental Validation of Modified Perturbation (NDM) Formulation**

Experimental verification demonstrating that the modified perturbation

formulation is capable of resolving internal structure of a dense scattering medium is

given in FIGS. 13 and 14. Tomographic measurements were performed at 780 nm using

20     the IRIS imaging system previously described. R.L. Barbour, R. Andronica, Q. Sha, H.L.

Graber, and I. Soller, "Development and evaluation of the IRIS-OPTIsoanner, a general-

purpose optical tomographic imaging system." *In Advance in Optical Imaging and

Photon Migration*, J.G. Fujimoto et al, ed., *Vol.* 21 of OSA Proceeding Series, pp. 251-

255, (1998) (the disclosures of which are incorporated herein by reference). The target

medium was a latex laboratory glove filled with 2% (v/v) Intralipid suspended from a

holder in a pendant position. Added to the glove were two 1 cm diameter plastic tubes

filled with varying concentrations of hemoglobin (Hb) in the amount of 5µm, 10µm,

5     20µm, and 40µm. A cross section of the phantom set-up is shown in FIG. 15. The pass-

through diameter of the IRIS imaging head was closed until gentle contact with the glove

was achieved. The diameter of the glove in the measurement plane was 6.7 cm. Above

and below this plane, the glove assumed an arbitrary geometry. Tomographic

measurements were performed using the same measurement geometry described for the

10   numerical studies. Optical measurements were performed in the presence and absence of

the included objects from which the relative intensity values were derived. The resultant

data vectors were then evaluated by equation (3) using a regularized CGD method

without weight matrix rescaling. The coefficient values for the reference medium used

were varied from 0.01 to 0.04 cm$^{-1}$ in $\mu_a$ and 10 to 20 cm$^{-1}$ in $\mu_s$.

15          Reconstructed $\mu_a$ and $D$ maps for each experiment with different concentrations of

hemoglobin in the two tubes using a specific reference medium are shown in FIG. 13.

Inspection reveals two well-resolved objects whose contrast in both coefficients increases

with increasing concentration of added absorber. Quantitatively, the dependence of

image contrast on absorber concentration is less than expected ($\delta\mu_a$ recovered = .005 vs.

20   $\delta\mu_a$ actual = .015 cm$^{-1}$) indicating perhaps either a self-shielding effect, limits of a first

order Born solution or both. Results shown in FIG. 14 demonstrate that images of similar

quality are derivable over a range of reference media, a result consistent with the above

described numerical studies.

27

## Discussion and Conclusions

The present invention describes and evaluates a new formulation for the inverse problem for imaging in highly scattering media. Motivating this development has been an appreciation of the expected limits imposed by practical measurements, especially as it

5 relates to the dependence of image accuracy on instrument calibration and the ability to specify an accurate reference medium. This concern arises because many of the anticipated clinical applications will require some level of accuracy in the computed coefficient values. An accurate solution will require an explicit accounting of various factors intrinsic to the detector (e.g., quantum efficiency, acceptance angle etc.), as well

10 as features specific to the target. This includes, in particular, the efficiency of contact with the target medium by the detector or intervening optical fibers that deliver and collect the optical signal. This is necessary because all model-based imaging schemes proposed for imaging in highly scattering media assume equivalency in detector efficiency for measured and computed values. Failure to account for such variables will

15 introduce error whose magnitude and stability could vary considerably depending on the specifics of the measuring device and target medium.

In principle, these uncertainties can be taken into account, although not without considerable effort for instrument design and added complexity of the forward modeling code. Generally speaking, such limitations are widely appreciated by many, both in this

20 and other imaging communities. The goal in identifying practical schemes is to devise strategies that are mainly insensitive to such uncertainties. Often a desirable starting point is to employ schemes that provide useful information based on some type of relative measurement. Previously, we described a back projection scheme that evaluated

relative detector data. R.L. Barbour, H. Graber, R. Aronson, and J. Lubowski, "Model for

3-D optical imaging of tissue," Int. Geosci and Remote Sensing Symp., (IGARSS), 2,

1395-1399 (1990) (the disclosures of which are incorporated herein by reference). H.L.

Graber, J. Chang, J. Lubowsky, R. Aronson and R.L. Barbour, "Near infrared absorption

5    imaging in dense scattering media by steady-state diffusion tomography", in Proc.

*Photon migration and imaging in random media and tissues "*, 1888, 372-386, (1993) (the

disclosures of which are incorporated herein by reference).  This formulation employed

model-based imaging operators, but produced solutions lacking physical units. The lack

of physical units (1) makes specific interpretation difficult, especially should multi-

10   wavelength measurements be considered, and (2) makes efforts to compute iterative

updates difficult.  However, this scheme however showed that in all cases tested, high

contrast images having excellent edge detection and object location were achievable. R.L.

Barbour, H. Graber, R. Aronson, and J. Lubowski, "Model for 3-D optical imaging of

tissue," Int. Geosci and Remote Sensing Symp., (IGARSS), 2, 1395-1399 (1990) (the

15   disclosures of which are incorporated herein by reference). H.L. Graber, J. Chang, J.

Lubowsky, R. Aronson and R.L. Barbour, "Near infrared absorption imaging in dense

scattering media by steady-state diffusion tomography", in Proc. *Photon migration and*

*imaging in random media and tissues "*, 1888, 372-386, (1993*)* (the disclosures of which

are incorporated herein by reference). H.L. Graber, J. Chang and R.L. Barbour "Imaging

20   of multiple targets in dense scattering media", in Proc. *Experimental and numerical*

*methods for solving ill-posed inverse problems:  Medical and non-medical applications*,

SPIE, 2570, 219-234, (1995) (the disclosures of which are incorporated herein by

reference).

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In subsequent studies we have identified that the expression evaluated using this method has a functional form of:

$$\left(\frac{\delta I}{I_0}\right)_i \left(\sum_{j=1}^{N} (W_r)_{ij}\right) = \sum_{j=1}^{N}\left((W_r)_{ij}(\delta x)_j\right) \tag{8}$$

for each source-detector pair where, i is the source-detector pair number, j is the element number and N is the number of elements. It is apparent that this expression is similar to the following equation, which is equation (3) with a different form,

$$\left(\frac{\delta I}{I_0}\right)_i (I_r)_i = \sum_{j=1}^{N}\left((W_r)_{ij}(\delta x)_j\right) \tag{9}$$

While it is evident the two expressions are not equivalent, a more careful examination reveals that the different quantities on the left hand side of Eqs. (8) and (9) (i.e.,, the sum of weights and the reference intensity for the i$^{th}$ source-detector pair) are closely related. The influence that different forms of the data vector have on image recovery is discussed subsequently.

Solution of the perturbation formulation requires specification of three input data sets. Two quantities, $I_r$ and $W_r$, are typically computed from a specified reference medium, and the third quantity is the measured response, I. Results presented in FIGS. 6 through 9 have explored the influence that errors in each of these quantities have on the quality of computed reconstructions for the original perturbation formulation (equation (1)). Most sensitive was the case where both quantities $I_r$ and $W_r$ are in error (c.f., test case 3 and FIG. 6). This suggests that the origin of excessive ill-conditioning can be traced to one or both of the quantities $I_r$ and $W_r$. When prior knowledge $W_r$ is assumed, errors in $I_r$ (test case 6) still produced highly unstable solutions (FIG. 8). On the other hand, when prior knowledge of the correct values of $I_r$ is assumed (test case 5), the

sensitivity to errors in $W_r$ is much less (FIG. 7), at least qualitatively. This strongly

suggests that the principal cause of instability can be traced to errors in $I_r$. It also

indicates that should error free measurement data be available, significant instability in

the solution domain would persist. The influence of systematic error in measurement was

5 explored in test case 7. Results in FIG. 9 showed that under conditions where prior

knowledge of $I_r$ and $W_r$ for the background is available, qualitatively accurate solutions

could be obtained even in the presence of 900% error. In the absence of this prior

knowledge, additional error due to this quantity further degraded image quality even in

those cases where the selected reference medium differed only minimally from the

10 background.

While we have demonstrated that the described reconstruction procedure can

significantly stabilize the computed reconstructions to errors in the reference medium,

and that the principal origin of solution instability in its absence is the result of to errors

in $I_r$, it is useful to gain further insight as to why this should occur. An important

15 difference between the two perturbation formulations is that equation (1) computes the

difference between two exponentially attenuated quantities, while equation (3) performs a

linear operation on an exponentially attenuated quantity. Because of the non-linear

relationship between the medium coefficient values and surface detector responses, small

errors in the former (the selected reference medium) can lead to large errors in the latter

20 (the computed intensity or weight associated with the selected reference medium).

Moreover, because the relationship is non-linear, such errors can be expected to

effectively distort the information content of the resultant data vector. The occurrence of

such distortion is shown in FIGS. 16 and 17. FIG. 16 shows the angle dependence of the

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relative detector response (i.e., the data vector) for a source bisecting the two inclusions

computed using reference media corresponding to row 3 and column 3 of FIG. 5.

Inspection of these plots clearly reveal a bimodal attenuation profile indicating the

presence of two buried objects, a finding consistent with its actual structure. In contrast,

5      this structure is almost completely absent from results derived using the original

perturbation formulation (see FIG. 17) even though the variation in range of the reference

medium is much less than that used in FIG. 16. This difference is most evident in results

given in FIG. 18 that shows the amplitude of the frequency spectrum of the

corresponding Fourier transforms. Comparison reveals that in the case where the selected

10     reference medium has an error only in $\mu_a$ of 0.02 cm$^{-1}$, this produces an error of

approximately 5 orders of magnitude in the amplitude of the frequency spectrum. This

error grows to approximately eight orders of magnitude for the case where the selected

reference medium has an error in $\mu_s$ of only 5 cm$^{-1}$. Given the magnitude of these errors,

the extreme sensitivity of the reconstruction results obtained from the original

15     perturbation equation is evident.

When we examined the computed data vector for the formulation based on

equation (7), we observed a pattern similar to that shown in FIG. 16, but with much

higher amplitude values. It is this close relationship that we believe accounts for why

previous reconstruction results derived using equation (8) also provided stable and

20     qualitatively accurate maps, even though the solutions lacked features important for

specific interpretation and iterative updates. R.L. Barbour, H. Graber, R. Aronson, and J.

Lubowski, "Model for 3-D optical imaging of tissue," Int. Geosci and Remote Sensing

Symp., (IGARSS), 2, 1395-1399 (1990) (the disclosures of which are incorporated herein

by reference). H.L. Graber, J. Chang, J. Lubowsky, R. Aronson and R.L. Barbour, "Near

infrared absorption imaging in dense scattering media by steady-state diffusion

tomography", in Proc. *Photon migration and imaging in random media and tissues ",*

*1888, 372-386, (1993)* (the disclosures of which are incorporated herein by reference).

5      Y.L. Graber, J. Chang and R.L. Barbour "Imaging of multiple targets in dense scattering

media", in Proc. *Experimental and numerical methods for solving ill-posed inverse*

*problems: Medical and non-medical applications*, SPIE, 2570, 219-234, (1995) (the

disclosures of which are incorporated herein by reference).

A further advantage of the current method compared to the previously described

10     SART-Type algorithm is that we are able to directly evaluate intensity difference values

for which no mismatches exist between the computed intensity values, $I_r$, and the

Jacobian matrix, $W_r$. Y.L. Graber, J. Chang and R.L. Barbour "Imaging of multiple

targets in dense scattering media", in Proc. *Experimental and numerical methods for*

*solving ill-posed inverse problems: Medical and non-medical applications*, SPIE, 2570,

15     219-234, (1995) (the disclosures of which are incorporated herein by reference). Not only

does this reduce systematic errors, but produces solutions that can be updated by iterative

methods. As reported here, error analysis studies have demonstrated that the current

methodology produces remarkable stable solutions having excellent qualitative accuracy.

An important goal shared by many investigators in the biomedical optics field is

20     the capacity to accurately quantify variations in optical coefficients in tissue. One

consequence of adopting the described reconstruction procedure is that the derived

solution will not converge to the actual value even with error free measurement data and

non-linear updates. Instead, as is evident from results shown in FIG. 4 and 5, they will

converge to a solution that is proportional to the true value throughout the image map.

Examination of the recovered values indicates that the value of this

proportionality coefficient depends strongly on the selected reference medium.

5    Interestingly, though, as shown in FIG. 19, the ratio of the computed coefficient values is

nearly constant over a broad range indicating that the relative error in the coefficients is

itself a constant. In fact, for the examples studied, we find that $(\delta\mu_a/\delta D)_{Reconstructed} \approx$

$(\delta\mu_a/\delta D)^{\frac{1}{2}}_{Original}$ over most of the range of reference values explored. In other examples

(results not shown), we have explored this relationship for a variety of perturbation

10   values with a similar range of reference media. In all cases, a constant error in the ratio of

the derived coefficients was obtained. The value of the proportionality constant,

however, varied depending on the magnitude and direction of the perturbation, but

remained within a relatively small range.

While it may be that case for some studies the restrictions imposed by the

15   described method may prove limiting, it is anticipated that there are many practical

situations where measurement of relative changes are nonetheless very useful. One

example of special interest is in the evaluation of dynamic imaging data.

Finally, from a mathematical perspective, the described methodology has the

effect of desensitizing the solution of boundary value problems to specific features of the

20   boundary. One practical consequence of this is that, unlike the standard perturbation

formulation, the current formulation is less sensitive to a detailed knowledge of the

external boundary of tissue, a quantity not easily measured.

While the instant invention has considered using of DC sources, it is expressly understood that the described methodology is extendable to other source conditions (e.g., time-harmonic and time-resolved measurements) and other inverse formulations (e.g., iterative gradient descent) and is extendable to other imaging modalities including,

5       ultrasound, radioscintigraphic and impedance imaging.

Although illustrative embodiments have been described herein in detail, those skilled in the art will appreciate that variations may be made without departing from the spirit and scope of this invention. Moreover, unless otherwise specifically stated, the terms and expressions used herein are terms of description and not terms of limitation,

10      and are not intended to exclude any equivalents of the system and methods set forth in the following claims.

What is claimed is:

1.    A method for imaging of the properties of a scattering target medium, comprising:

generating a first vector of measured data and a second vector of measured data, the first vector of measured data being indicative of energy emerging from a target medium, the second vector of measured data being indicative of energy emerging from a target medium, the emerging energy substantially originating from at least one source directing the energy into the target medium;

normalizing the first and second vectors of measured data; and

solving a modified perturbation formulation of the radiation transport inverse problem for a relative change between a known property of a reference medium and the corresponding unknown property of a target medium, wherein the modified perturbation equation relates the normalized measured data and a vector of reference data for the known reference medium to the relative change in the property, the vector of reference data being indicative of energy emerging from the known reference medium.

2.    The method of claim 1 wherein the normalization of the first and second vectors of measured data comprises determining the difference between the first and second vectors of measured data relative to the second vector of measured data.

3.    The method of claim 1 wherein the modified perturbation equation has the following form:

$$\left(\delta \mathbf{I}_r\right)_i = \left[\frac{I_i - \left(\mathbf{I}_0\right)_i}{\left(\mathbf{I}_0\right)_i}\right]\left(\mathbf{I}_r\right)_i ; \text{ and}$$

$$\mathbf{W}_r \cdot \delta \mathbf{x} = \delta \mathbf{I}_r ,$$

where $\delta \mathbf{x}$ is a vector of the relative changes between a known property of the reference medium and the corresponding unknown property of a target medium, for corresponding volume elements of the reference medium and the target medium, the volume elements being an imaginary grid of contiguous regions forming a representation of the target medium and reference medium, $\mathbf{W'}_r$ is a weight matrix describing the influence that each of a plurality of volume elements of the reference medium has on energy emerging at a point on the reference medium, $I_r$ is the vector of reference data indicative of energy emerging from the reference medium, I is the first vector of measured data and $I_0$ is the second vector of measured data.

4.      The method of claim 1 wherein the normalization of the first and second sets of measured data comprise determining the natural logarithm of the quotient of the first set of measured data and the second set of measured data.

5.      The method of claim 1 wherein the modified perturbation equation has the following form:

$$\left(\delta \mathbf{I}'\right)_i = \ln\frac{I_i}{\left(\mathbf{I}_0\right)_i};$$

$$\left(\mathbf{W}_r'\right)_{ij} = \frac{\left(\mathbf{W}_r\right)_{ij}}{\left(\mathbf{I}_r\right)_i};$$

$$\delta \mathbf{I}' = \mathbf{W}_r'\delta \mathbf{x}$$

37

where $\delta x$ is a vector of the relative changes between a known property of the reference medium and the corresponding unknown property of a target medium for corresponding volume elements of the reference medium and the target medium, the volume elements being an imaginary grid of contiguous, nonoverlapping regions forming a representation of the target medium and reference medium, $W_r$ is a weight matrix describing the influence that each of a plurality of volume elements of the reference medium has on energy emerging at a point on the reference medium, where $I_r$ is the vector of reference data indicative of energy emerging from the reference medium, $I$ is the first vector of measured data and $I_0$ is the second vector of measured data.

6.　　The method of claim 1 wherein the property is at least one of an absorption coefficient and a scattering coefficient.

7.　　The method of claim 1 wherein the first vector of measured data and second vector of measured data are obtained from one target.

8.　　The method of claim 1 wherein the first vector of measured data is obtained from a first target and the second vector of measured data is obtained from a second target.

9.　　The method of claim 1 wherein the first vector of measured data is obtained at a first instant in time and the second vector of measured data is obtained at a second instant in time.

10.    The method of claim 1 wherein the first vector of measured data is obtained at a first instant in time and the second vector of measured data is a time averaged mean of a plurality of measurements.

11.    A method of claim 1 further comprising generating an image representing the cross-sectional relative changes in the property.

12.    A system for imaging of the properties of a scattering target medium, comprising:

means for generating a first vector of measured data and a second vector of measured data, the first vector of measured data being indicative of energy emerging from a target medium, the second vector of measured data being indicative of energy emerging from a target medium, the emerging energy substantially originating from at least one source directing the energy into the target medium;

means for normalizing the first and second vectors of measured data; and

means for solving a modified perturbation formulation of the radiation transport inverse problem for a relative change between a known property of a reference medium and the corresponding unknown property of a target medium, wherein the modified perturbation equation relates the normalized measured data and a vector of reference data for the known reference medium to the relative change in the property, the vector of reference data being indicative of energy emerging from the known reference medium.

39

13.    The system of claim 12 wherein the normalization of the first and second vectors of measured data comprises determining the difference between the first and second vectors of measured data relative to the second vector of measured data.

14.    The system of claim 12 wherein the modified perturbation equation has the following form:

$$(\delta I_r)_i = \left[\frac{I_i - (I_0)_i}{(I_0)_i}\right](I_r)_i ; \text{ and}$$

$$W_r \cdot \delta x = \delta I_r ,$$

where $\delta x$ is a vector of the relative changes between a known property of the reference medium and the corresponding unknown property of a target medium, for corresponding volume elements of the reference medium and the target medium, the volume elements being an imaginary grid of contiguous regions forming a representation of the target medium and reference medium, $W'_r$ is a weight matrix describing the influence that each of a plurality of volume elements of the reference medium has on energy emerging at a point on the reference medium, $I_r$ is the vector of reference data indicative of energy emerging from the reference medium, $I$ is the first vector of measured data and $I_0$ is the second vector of measured data.

15.    The system of claim 12 wherein the normalization of the first and second sets of measured data comprise determining the natural logarithm of the quotient of the first set of measured data and the second set of measured data.

16.    The system of claim 12 wherein the modified perturbation equation has

the following form:

$$\left(\delta \mathbf{I}'\right)_i = \ln \frac{I_i}{\left(\mathbf{I_o}\right)_i};$$

$$\left(\mathbf{W}_r'\right)_{ij} = \frac{\left(\mathbf{W}_r\right)_{ij}}{\left(\mathbf{I}_r\right)_i};$$

$$\delta \mathbf{I}' = \mathbf{W}_r' \delta \mathbf{x}$$

where δx is a vector of the relative changes between a known property of the

reference medium and the corresponding unknown property of a target medium for

corresponding volume elements of the reference medium and the target medium, the

volume elements being an imaginary grid of contiguous, nonoverlapping regions forming

a representation of the target medium and reference medium, $W_r$ is a weight matrix

describing the influence that each of a plurality of volume elements of the reference

medium has on energy emerging at a point on the reference medium, where $I_r$ is the

vector of reference data indicative of energy emerging from the reference medium, I is

the first vector of measured data and $I_0$ is the second vector of measured data.

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*[Continued on next page]*

(54) **Title: IMAGING OF SCATTERING MEDIA USING RELATIVE DETECTOR VALUES**
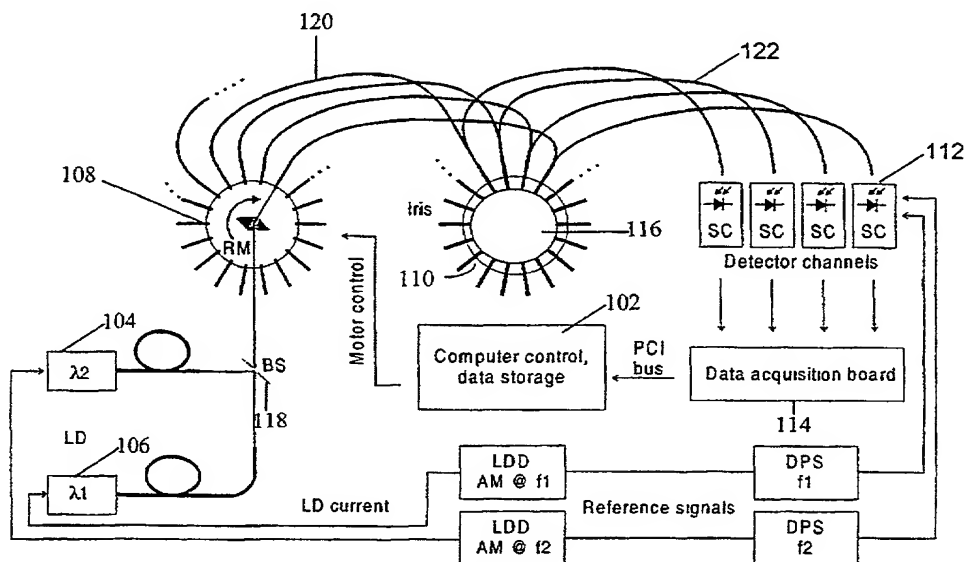
(57) **Abstract:** A method for imaging of a scattering target medium using a modified perturbation formulation of the radiation transport equation wherein normalized measured values are used to recover a relative difference in absorption and/or scattering properties based on the normalized measured values with respect to a reference medium. The modified perturbation formulation provides enhanced stability, reduces the sensitivity of solution to variations between the target and reference media, produces solutions having physical units and reduces the need for absolute detector calibration. Moreover, the modified perturbation equation lends itself to the detection and imaging of dynamic properties of the scattering medium.

WO 01/20546 A2

FIG. 1

FIG. 2B



FIG. 2A

| # | Test Case Formulation | I | $I_0$ | $I_r$ | $W_r$ | $\beta$ | Inverse Algorithms | Result Presented |
|---|---|---|---|---|---|---|---|---|
| 1 | $W_r\delta x = \left(\dfrac{I-I_0}{I_0}\right)I_r$ | C | C | V | V | / | CGD | 6x6 Matrix |
| 2 | $W_r\delta x = \left(\dfrac{I-I_0}{I_0}\right)I_r$ | C | C | V | V | / | CGD + WMR | 6x6 Matrix |
| 3 | $W_r\delta x = I - I_r$ | C | / | V | V | / | CGD | 5x5 Matrix |
| 4 | $W_r\delta x = I - I_r$ | C | / | V | V | / | CGD + WMR | 5x5 Matrix |
| 5 | $W_r\delta x = I - I_b$ | C | / | C | V | / | CGD | 6x6 Matrix |
| 6 | $W_b\delta x = I - I_r$ | C | / | V | C | / | CGD | 5x5 Matrix |
| 7 | $W_b\delta x = \beta I - I_b$ | C | / | C | C | V | CGD | 3x3 Matrix |
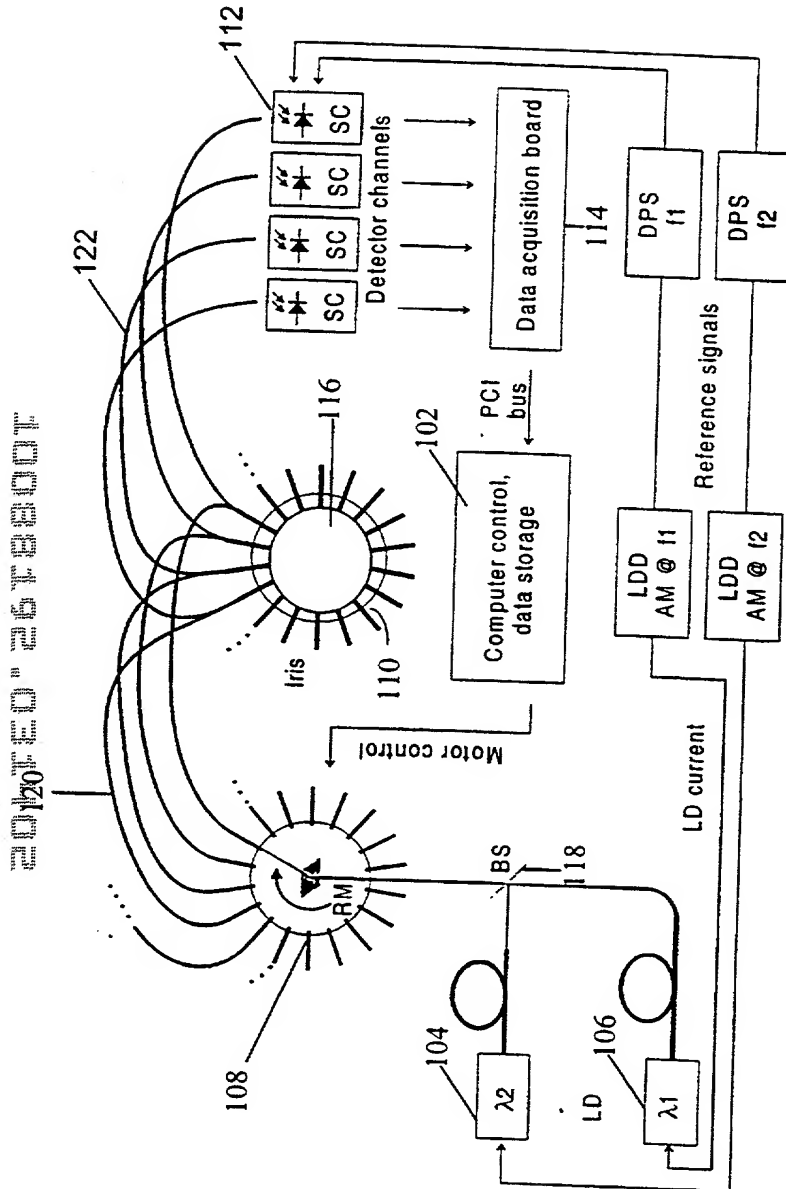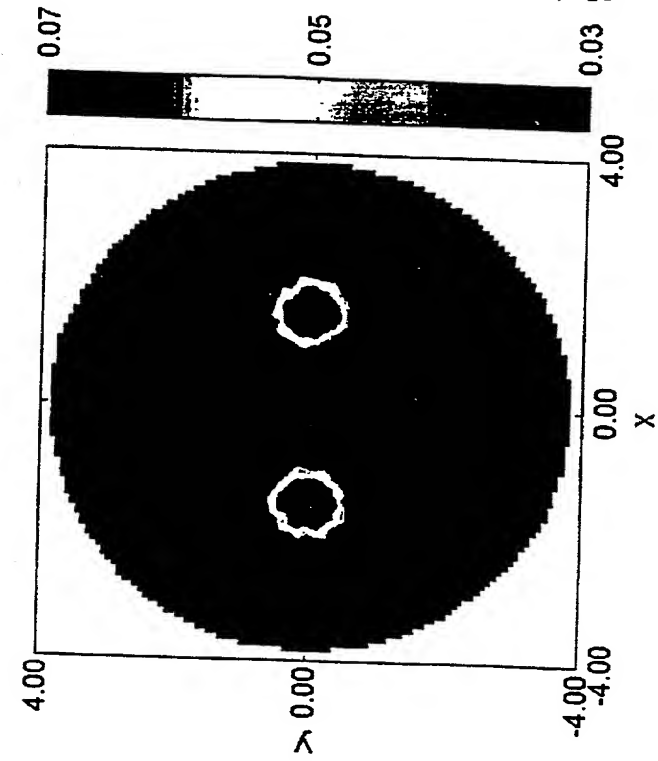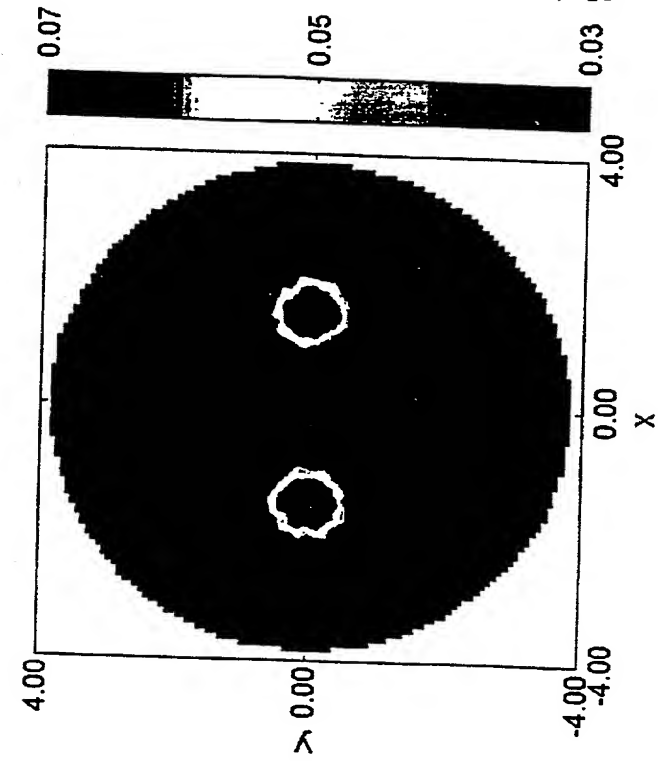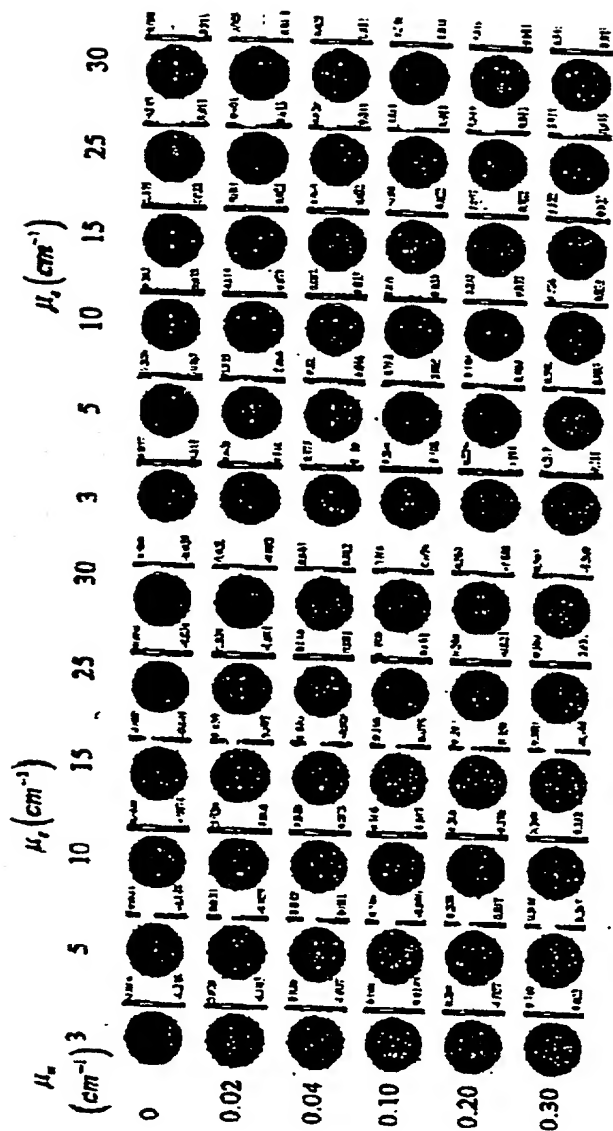
*The Parameters Involved* spans columns I, $I_0$, $I_r$, $W_r$, $\beta$.

**FIG. 3**

FIG. 5A

FIG. 5B

FIG. 4A



FIG. 4B

FIG. 6A



FIG. 6B

$\mu_s'(cm^{-1})$

$\mu_s'(cm^{-1})$

$\mu_a$ (cm$^{-1}$)
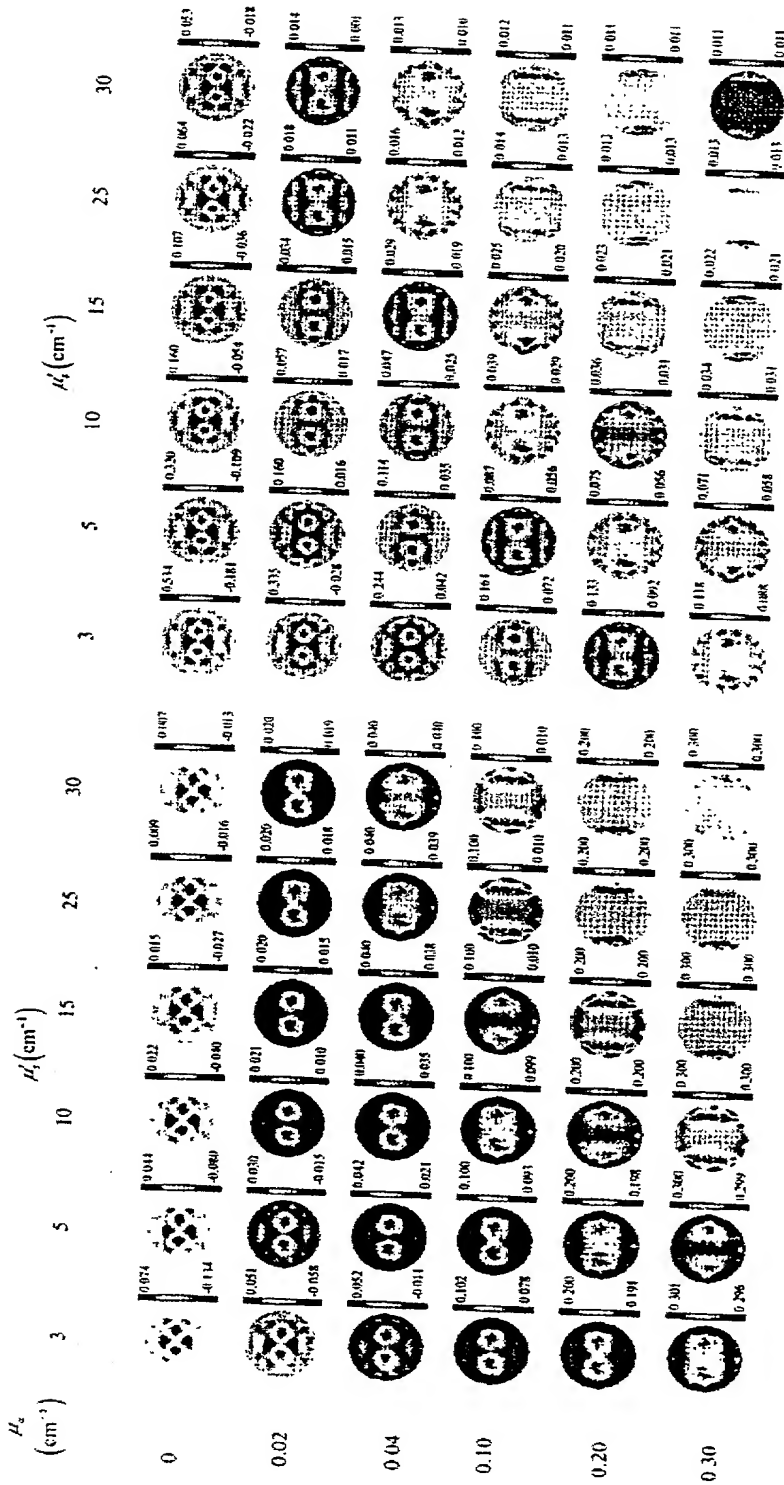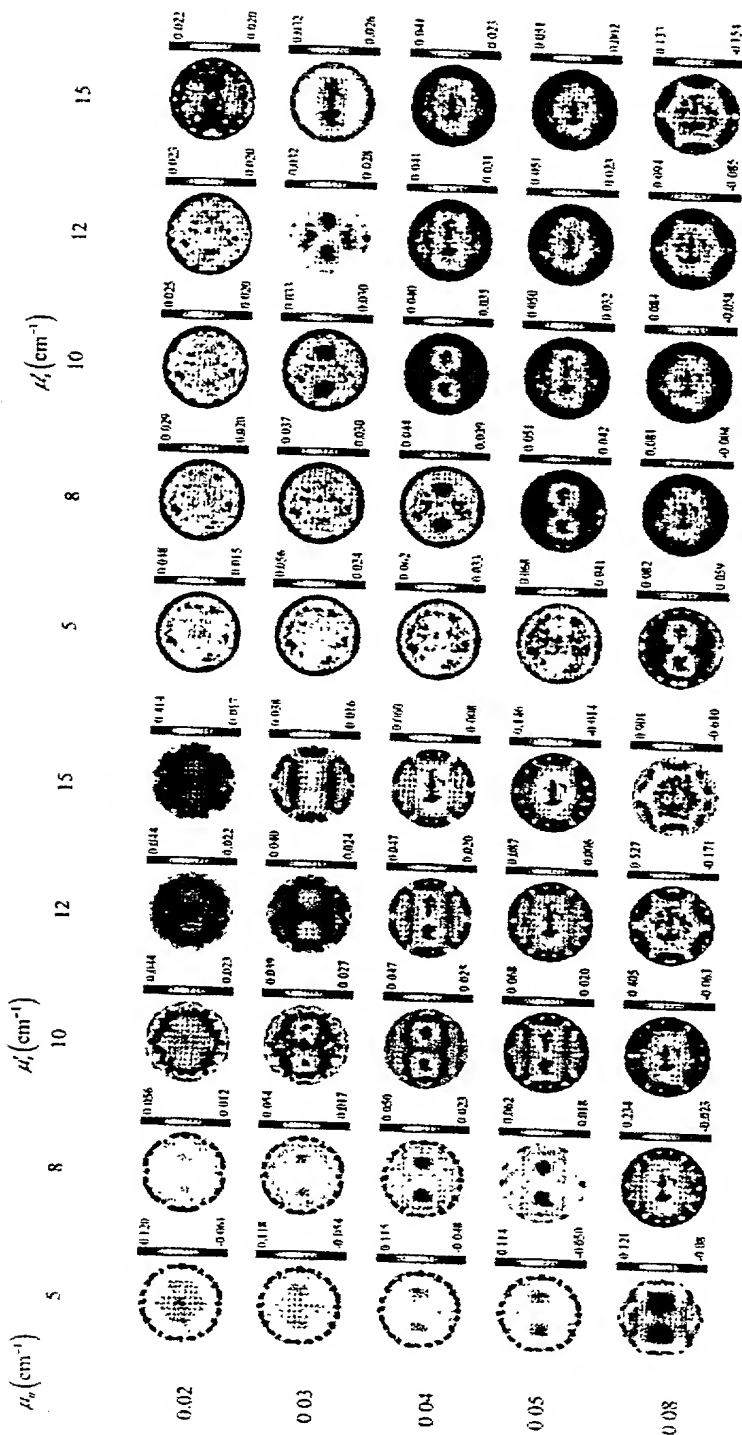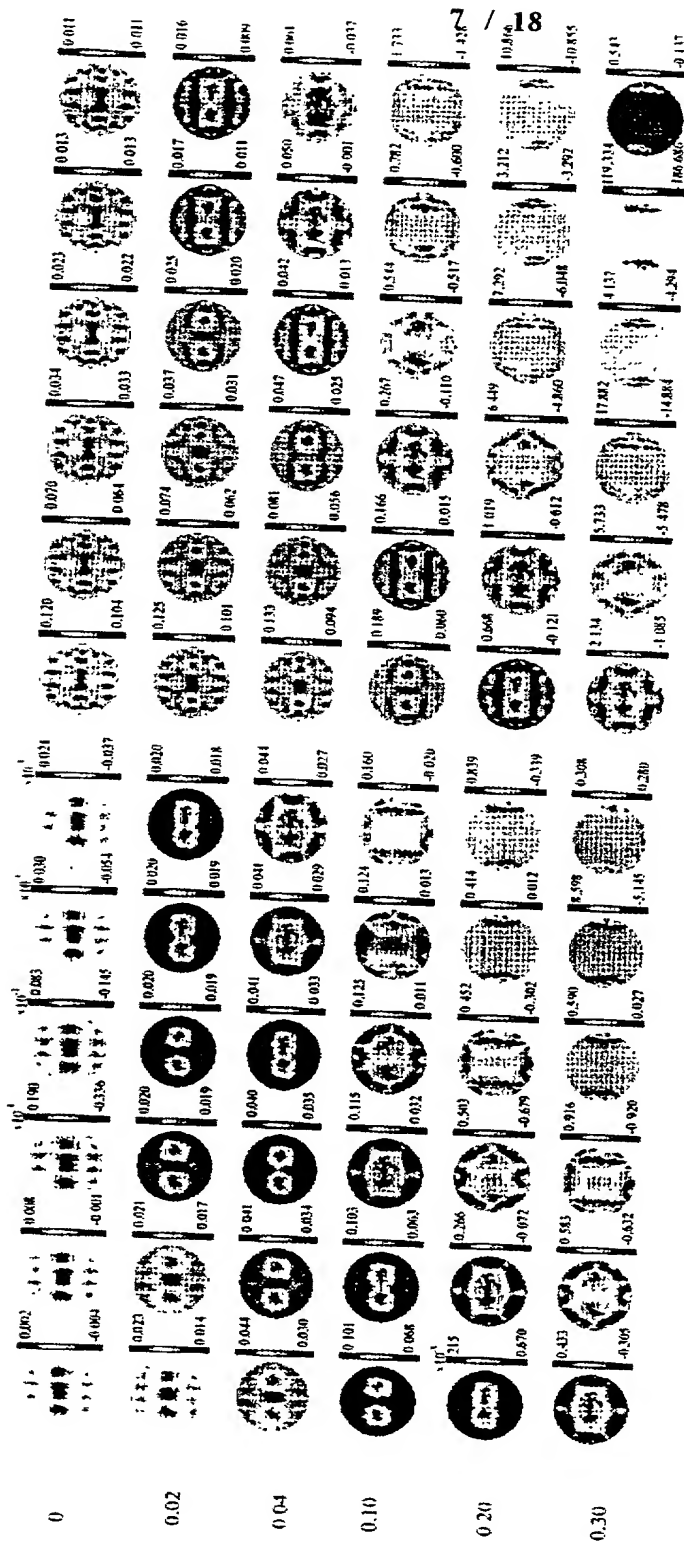
FIG. 7A

FIG. 7B
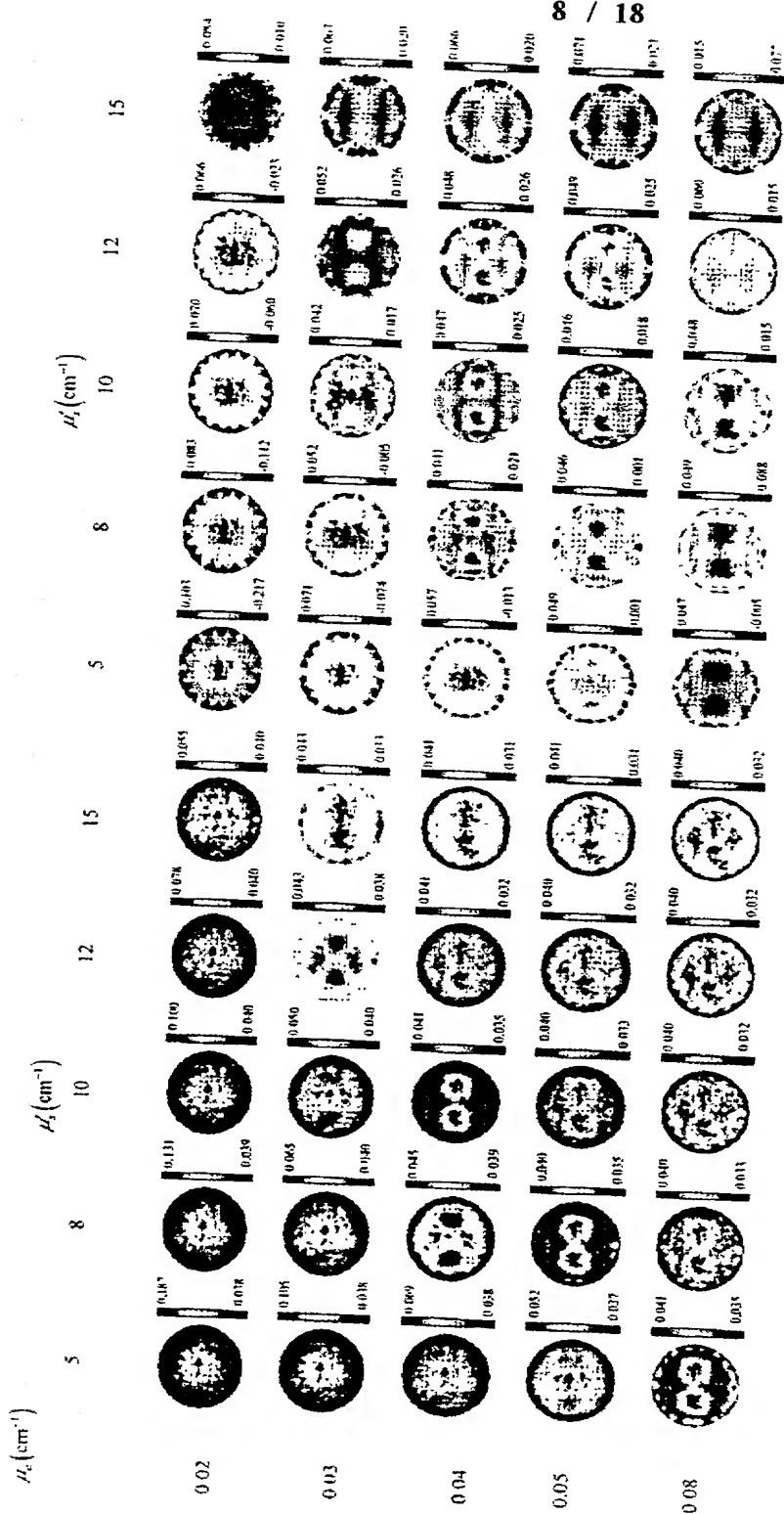
FIG. 8A

FIG. 8B
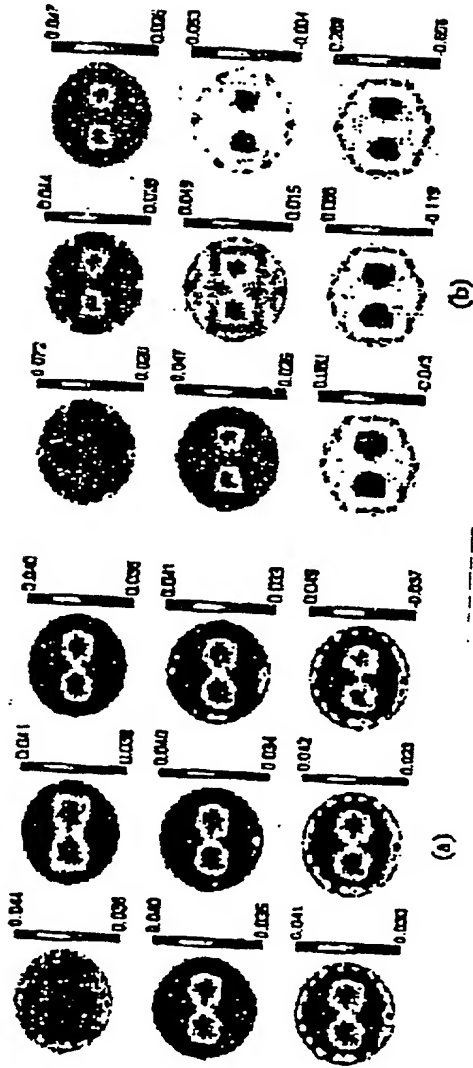
FIG. 9A

FIG. 9B

Constant Calibration Errors

| -50% | -10% | 0% |
|------|------|-----|
| 10% | 25% | 50% |
| 100% | 200% | 900% |

**FIG. 10**

Ua                                                    D

| Image RSME | | | | | | Image RSME | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1.2024 | 1.0805 | 1.0229 | 1.0113 | 1.0048 | 1.0036 | 3.4978 | 1.8461 | 0.7665 | 0.6061 | 0.6689 | 0.7096 |
| 0.6449 | 0.5520 | 0.5181 | 0.5089 | 0.5023 | 0.5010 | 2.5947 | 1.0714 | 0.1394 | 0.3617 | 0.6149 | 0.6787 |
| 0.2055 | 0.0881 | 0.0791 | 0.0861 | 0.0910 | 0.0917 | 2.3307 | 0.9784 | 0.1396 | 0.3682 | 0.6188 | 0.6825 |
| 1.4762 | 1.5126 | 1.5330 | 1.5369 | 1.5385 | 1.5386 | 2.1879 | 0.9450 | 0.1638 | 0.3823 | 0.6260 | 0.6876 |
| 4.0360 | 4.0585 | 4.0677 | 4.0687 | 4.0690 | 4.0690 | 2.0802 | 0.9036 | 0.1742 | 0.3924 | 0.6289 | 0.6897 |
| 6.5828 | 6.5959 | 6.6002 | 6.6005 | 6.6005 | 6.6005 | 1.9768 | 0.8595 | 0.1795 | 0.3980 | 0.6305 | 0.6909 |

| Object Contrast (True Contrast Value = 0.02 cm$^{-1}$) | | | | | | Object Contrast (True Contrast Value = 0.0332 cm$^{-1}$) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 0.1418 | 0.0849 | 0.0425 | 0.0284 | 0.0170 | 0.0142 | 0.4091 | 0.2444 | 0.1222 | 0.0819 | 0.0491 | 0.0410 |
| 0.0899 | 0.0425 | 0.0132 | 0.0066 | 0.0025 | 0.0017 | 0.2466 | 0.1155 | 0.0341 | 0.0165 | 0.0064 | 0.0048 |
| 0.0639 | 0.0262 | 0.0076 | 0.0035 | 0.0008 | 0.0005 | 0.1723 | 0.0675 | 0.0189 | 0.0096 | 0.0029 | 0.0021 |
| 0.0315 | 0.0121 | 0.0020 | 0.0007 | 0.0001 | 0.0000 | 0.0779 | 0.0313 | 0.0071 | 0.0036 | 0.0004 | 0.0003 |
| 0.0141 | 0.0037 | 0.0004 | 0.0001 | 0.0000 | 0.0000 | 0.0431 | 0.0133 | 0.0031 | 0.0006 | 0.0001 | 0.0001 |
| 0.0063 | 0.0017 | 0.0001 | 0.0000 | 0.0000 | 0.0000 | 0.0219 | 0.0098 | 0.0009 | 0.0002 | 0.0000 | 0.0000 |

| Edge Resolution (Actual FWHM = 1 cm) | | | | | | Edge Resolution (Actual FWHM = 1 cm) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1.2656 | 1.2656 | 1.2656 | 1.2656 | 1.2656 | 1.2656 | 1.1707 | 1.1707 | 1.1707 | 1.1707 | 1.1707 | 1.1707 |
| 1.3922 | 1.5187 | 1.6137 | 1.7402 | 2.0250 | 2.0566 | 1.2340 | 1.2978 | 1.2973 | 1.3605 | 1.6137 | 1.6453 |
| 1.5504 | 1.6137 | 1.8035 | 2.0566 | 2.1832 | 1.5187 | 1.2973 | 1.2973 | 1.4238 | 1.6453 | 1.3605 | 1.1074 |
| 1.7402 | 2.0250 | 2.1832 | 1.3289 | 1.1391 | 1.0441 | 1.3605 | 1.6137 | 1.3605 | 1.2973 | 0.9809 | 0.9492 |
| 2.1516 | 2.0883 | 1.3289 | 1.0441 | 0.6328 | 0.6645 | 1.6453 | 1.3605 | 1.2023 | 0.9492 | 0.6012 | 0.6645 |
| 2.1832 | 1.3605 | 1.0441 | 0.6328 | 0.6645 | 0.3480 | 1.3605 | 1.2656 | 0.9492 | 0.3480 | 0.6328 | 0.2215 |

FIG. 11

Ua                                              D

| Image RSME | | | | | | Image RSME | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1.1171 | 1.0615 | 1.0272 | 1.0173 | 1.0100 | 1.0082 | 2.9455 | 1.4274 | 0.4252 | 0.3957 | 0.5926 | 0.6555 |
| 0.5662 | 0.5251 | 0.5061 | 0.5029 | 0.5020 | 0.5019 | 2.6397 | 1.1522 | 0.1382 | 0.3447 | 0.6095 | 0.6763 |
| 0.1143 | 0.0560 | 0.0511 | 0.0586 | 0.0598 | 0.0748 | 2.4602 | 1.0394 | 0.1042 | 0.3594 | 0.6135 | 0.6750 |
| 1.4935 | 1.5003 | 1.5152 | 1.5359 | 1.5373 | 1.5350 | 2.2413 | 0.9426 | 0.1317 | 0.3578 | 6.9283 | 15.892 |
| 4.0029 | 4.0296 | 4.0678 | 4.0614 | 4.0810 | 4.6830 | 2.0733 | 0.9074 | 2.9287 | 23.021 | 59.515 | 66.122 |
| 6.5353 | 6.5962 | 6.5889 | 6.5719 | 9.4904 | 24.8398 | 1.9857 | 1.0638 | 30.856 | 58.531 | 73.635 | 78.807 |

| Object Contrast (True Contrast Value = $0.02$ cm$^{-1}$) | | | | | | Object Contrast (True Contrast Value = $0.0332$ cm$^{-1}$) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 0.0017 | 0.0010 | 0.0005 | 0.0003 | 0.0002 | 0.0002 | 0.3790 | 0.2274 | 0.1137 | 0.0758 | 0.0455 | 0.0379 |
| 0.0044 | 0.0053 | 0.0078 | 0.0089 | 0.0105 | 0.0111 | 0.2697 | 0.1377 | 0.0474 | 0.0239 | 0.0088 | 0.0056 |
| 0.0127 | 0.0157 | 0.0199 | 0.0221 | 0.0153 | 0.0105 | 0.2035 | 0.0938 | 0.0281 | 0.0112 | 0.0057 | 0.0051 |
| 0.0446 | 0.0531 | 0.0376 | 0.0056 | 0.0004 | 0.0017 | 0.1138 | 0.0419 | 0.0142 | 0.0106 | 0.0141 | 0.6339 |
| 0.1072 | 0.0724 | 0.0003 | 0.0035 | 0.0001 | 0.0002 | 0.0503 | 0.0277 | 0.0145 | 1.9047 | 6.4243 | 6.8546 |
| 0.1169 | 0.0080 | 0.0044 | 0.0015 | 0.0050 | 0.1918 | 0.0433 | 0.0289 | 2.4170 | 6.2687 | 7.6970 | 8.7233 |

| Edge Resolution (Actual FWHM = 1 cm) | | | | | | Mean FWHM (Actual FWHM = 1 cm) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 3.2590 | 3.2590 | 3.2590 | 3.2590 | 3.2590 | 3.2590 | 0.7594 | 0.7594 | 0.7594 | 0.7594 | 0.7594 | 0.7594 |
| 0.5062 | 0.6012 | 0.6328 | 0.6961 | 0.6328 | 0.6328 | 0.7594 | 0.7594 | 0.7910 | 0.7594 | 0.7594 | 0.4746 |
| 0.5379 | 0.6328 | 0.6645 | 0.6328 | 0.5062 | 0.4113 | 0.7910 | 0.7910 | 0.8227 | 0.4746 | 0.4113 | 0.3797 |
| 0.6961 | 0.6328 | 0.4430 | 0.3797 | 0.1582 | 0.2531 | 0.7594 | 0.7277 | 0.4113 | 0.4113 | 0.2215 | 1.8035 |
| 0.6012 | 0.4746 | 2.8477 | 0.2531 | 0.1898 | 0.1898 | 0.4746 | 0.3797 | 0.1898 | 0.3480 | 3.0059 | 3.0059 |
| 0.5062 | 0.4113 | 0.2215 | 0.1898 | 0.3797 | 0.0949 | 0.3797 | 0.3164 | 0.3797 | 3.0059 | 3.0059 | 3.4488 |

**FIG. 12**
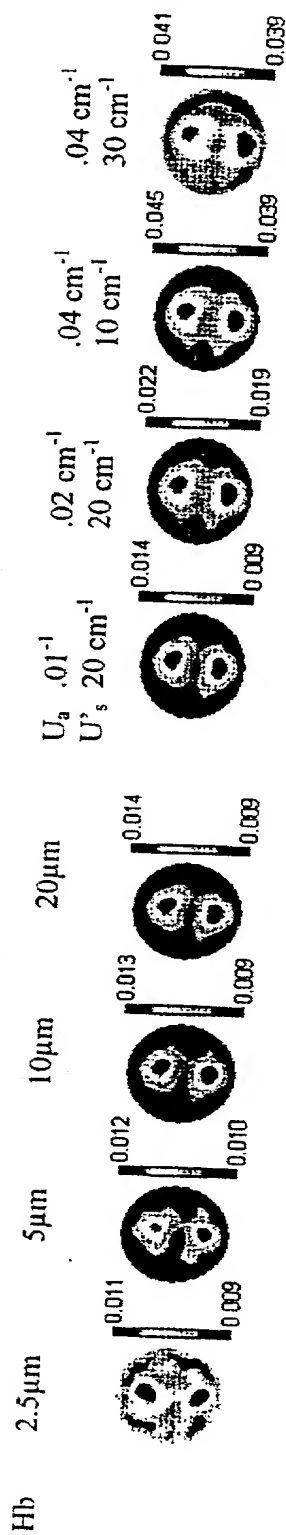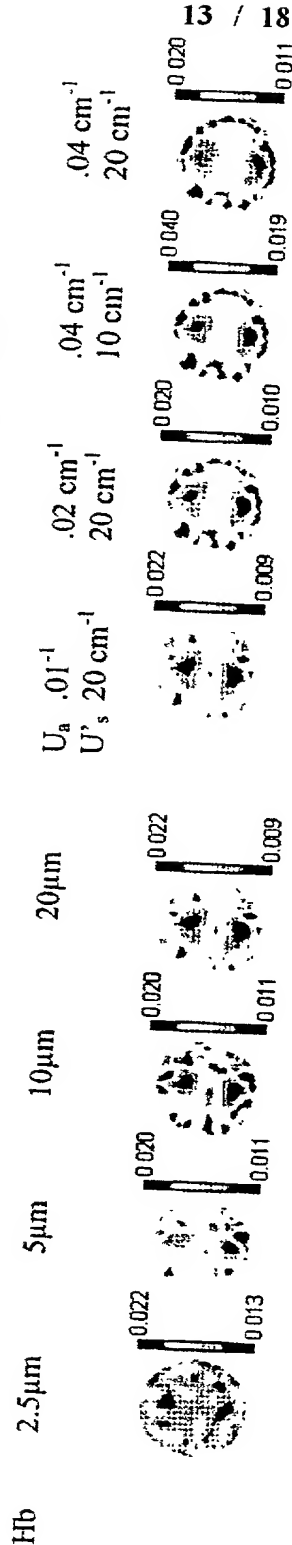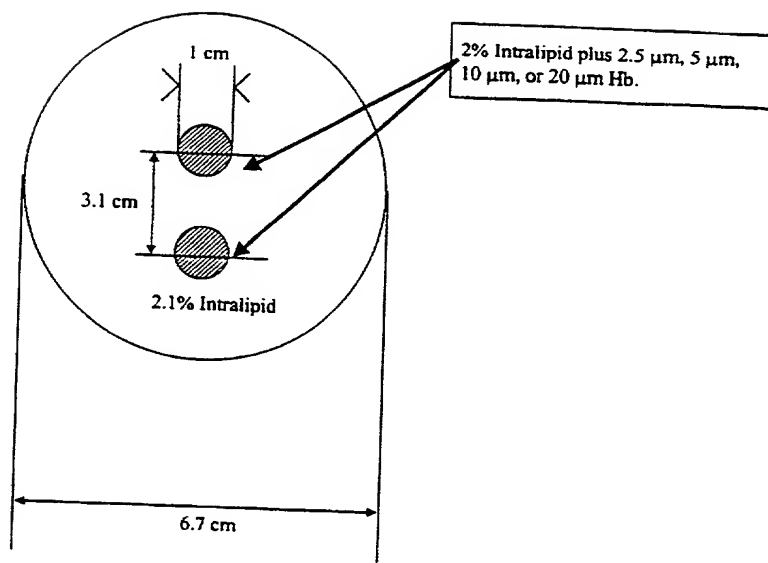
FIG. 13A

FIG. 13B

FIG. 14A

FIG. 14B

FIG. 15
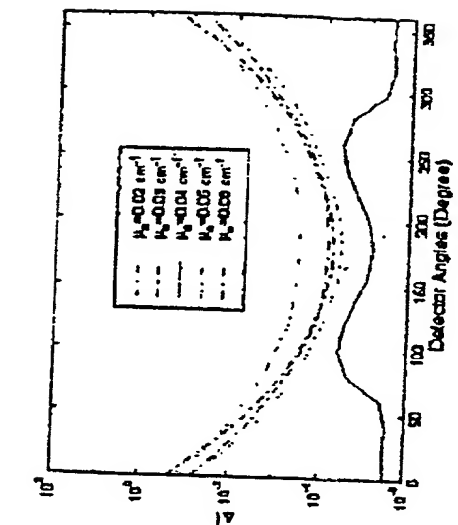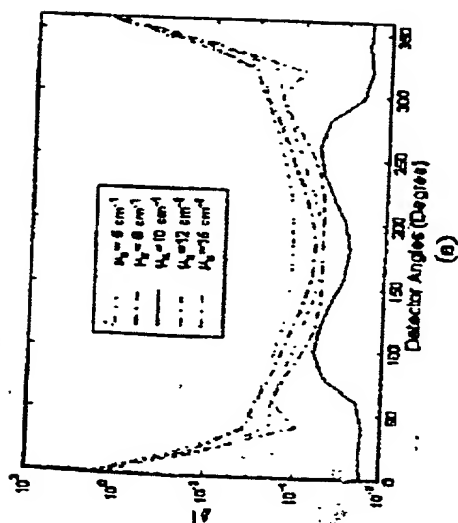
FIG. 16B



FIG. 16A
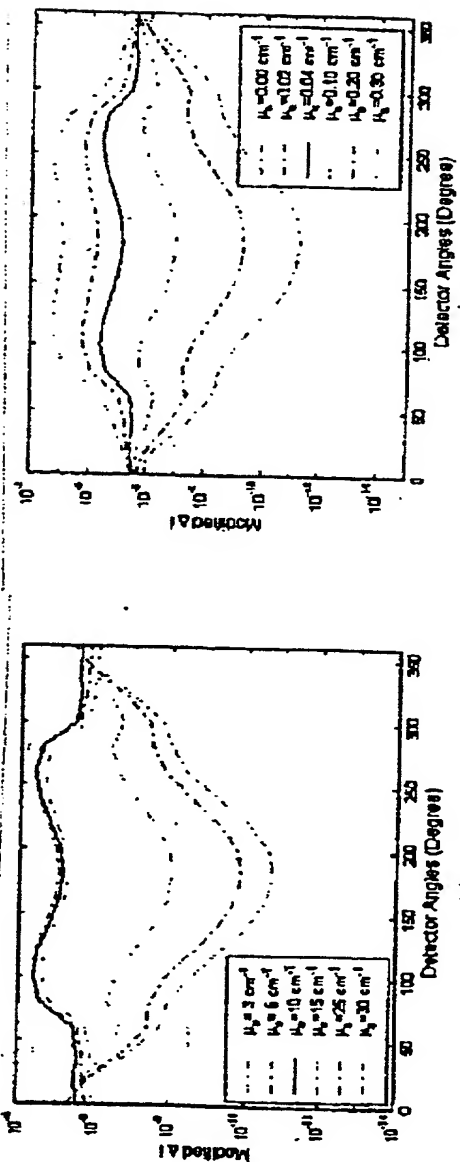
FIG. 17B

FIG. 17A
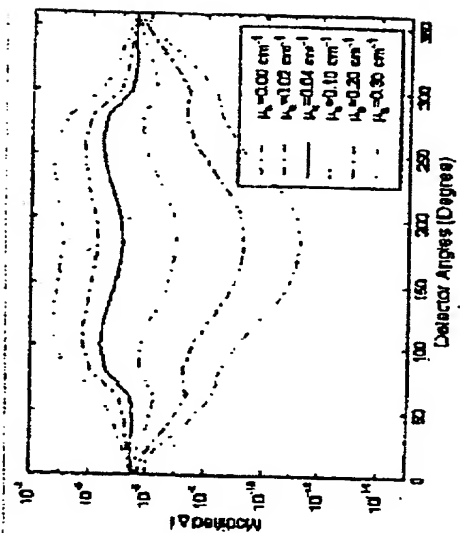
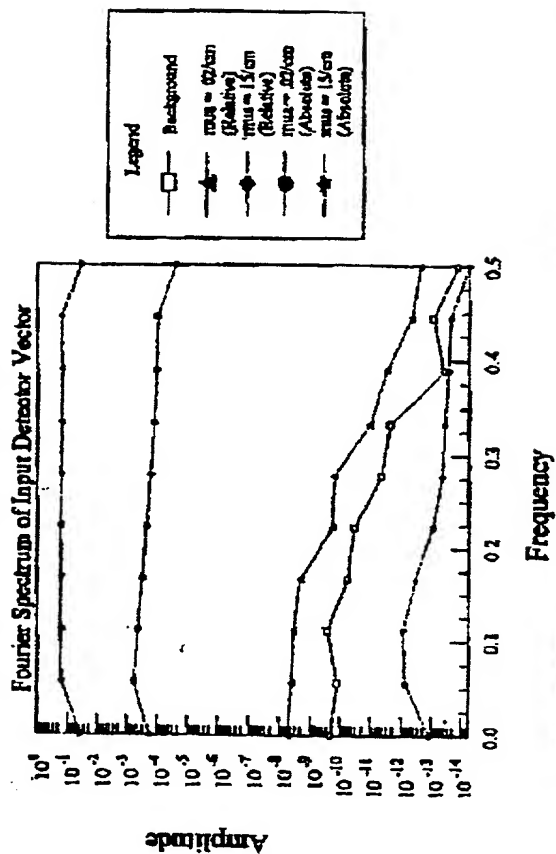FIG. 18

Original ratio = $\delta\mu/\delta D = 0.02/0.0332 = 0.6024$
$(\delta\mu_a/\delta D)^{1/2} = 0.3626$

$\mu_s$' (cm$^{-1}$)

|            | 7      | 5      | 10     | 15     | 25     | 30     |
|------------|--------|--------|--------|--------|--------|--------|
| 0.00       | 0.3427 | 0.3435 | 0.3441 | 0.3429 | 0.3427 | 0.3429 |
| 0.02       | 0.3627 | 0.3682 | 0.3882 | 0.4000 | 0.3846 | 0.3469 |
| 0.04       | 0.3715 | 0.3887 | 0.4042 | 0.3608 | 0.2758 | 0.2380 |
| 0.10       | 0.4048 | 0.3817 | 0.2816 | 0.1891 | 0.2000 | 0.0000 |
| 0.20       | 0.3463 | 0.2761 | 0.1212 | 0.1428 | 0.0000 | 0.0000 |
| 0.30       | 0.2863 | 0.1683 | 0.1000 | 0.0000 | -NAN   | -NAN   |

$\mu_a$ (cm$^{-1}$)

**FIG. 19**

## COMBINED DECLARATION AND POWER OF ATTORNEY FOR
## ORIGINAL, DESIGN, NATIONAL STAGE OF PCT, SUPPLEMENTAL
## DIVISIONAL, CONTINUATION OR CONTINUATION-IN-PART APPLICATION

As a below name inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

IMAGING OF SCATTERING MEDIA USING RELATIVE DETECTOR VALUES
the specification of which

      a. [ ]   is attached hereto

      b. [ ]   was filed on _____ as application Serial No. _____ and was amended on
         _____. (if applicable).

### PCT FILED APPLICATION ENTERING NATIONAL STAGE

      c. [x]   was described and claimed in International Application No. PCT/US00/25156 filed on 14
         September 2000 and as amended on _____. (if any).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

I hereby specify the following as the correspondence address to which all communications about this application are to be directed:

      SEND CORRESPONDENCE TO:     MORGAN & FINNEGAN, L.L.P
                                    345 Park Avenue
                                    New York, N.Y.  10154

      DIRECT TELEPHONE CALLS TO:   Tod M. Melgar
      (212) 758-4800

     [ ] I hereby claim foreign priority benefits under Title 35, United States Code § 119(a)-(d) or under § 365(b) of any foreign application(s) for patent or inventor's certificate or under § 365(a) of any PCT international application(s) designating at least one country other than the U.S. listed below and also have identified below such foreign application(s) for patent or inventor's certificate or such PCT international application(s) filed by me on the same subject matter having a filing date within twelve (12) months before that of the application on which priority is claimed:

     [ ] The attached 35 U.S.C. § 119 claim for priority for the application(s) listed below forms a part of this declaration.

577200_1

| Country/PCT | Application Number | Date of filing (day, month, yr) | Date of Issue (day, month, yr) | Priority Claimed |
|---|---|---|---|---|
| | | | | [ ] YES [ ] NO |
| | | | | [ ] YES [ ] NO |
| | | | | [ ] YES [ ] NO |

[X] I hereby claim the benefit under 35 U.S.C. § 119(e) of any U.S. provisional application(s) listed below.

| Provisional Application No. | Date of Filing (day, month, yr) |
|---|---|
| 60/153,769 | 14 September 1999 |
| 60/153,926 | 14 September 1999 |
| 60/154,099 | 15 September 1999 |

### ADDITIONAL STATEMENTS FOR DIVISIONAL, CONTINUATION OR CONTINUATION-IN-PART OR PCT INTERNATIONAL APPLICATION(S) (DESIGNATING THE U.S.)

I hereby claim the benefit under Title 35, United States Code § 120 of any United States application(s) or under § 365(c) of any PCT international application(s) designating the U.S. listed below.

| US/PCT Application Serial No. | Filing Date | Status (patented, pending, abandoned)/ U.S. application no. assigned (For PCT) |
|---|---|---|
| US/PCT Application Serial No. | Filing Date | Status (patented, pending, abandoned)/ U.S. application no. assigned (For PCT) |

[ ] In this continuation-in-part application, insofar as the subject matter of any of the claims of this application is not disclosed in the above listed prior United States or PCT international application(s) in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, § 1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or Imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

-2-

577200_1

I hereby appoint the following attorneys and/or agents with full power of substitution and revocation, to prosecute this application, to receive the patent, and to transact all business in the Patent and Trademark Office connected therewith: John A. Diaz (Reg. No. 19,550), John C. Vassil (Reg. No. 19,098), Alfred P. Ewert (Reg. No. 19,887), David H. Pfeffer (Reg. No. 19,825), Harry C. Marcus (Reg. No. 22,390), Robert E. Paulson (Reg. No. 21,046), Stephen R. Smith (Reg. No. 22,615), Kurt E. Richter (Reg. No. 24,052), J. Robert Dailey (Reg. No. 27,434), Eugene Moroz (Reg. No. 25,237), John F. Sweeney (Reg. No. 27,471), Arnold I. Rady (Reg. No. 26,601), Christopher A. Hughes (Reg. No. 26,914), William S. Feiler (Reg. No. 26,728), Joseph A. Calvaruso (Reg. No. 28,287), James W. Gould (Reg. No. 28,859), Richard C. Komson (Reg. No. 27,913), Israel Blum (Reg. No. 26,710), Bartholomew Verdirame (Reg. No. 28,483), Maria C.H. Lin (reg. No. 29,323), Joseph A. DeGirolamo (Reg. No. 28,595), Michael P. Dougherty (Reg. No. 32,730), Seth J. Atlas (Reg. No. 32,454), Andrew M. Riddles (Reg. No. 31,657), Bruce D. DeRenzi (Reg. No. 33,676), Michael M. Murray (Reg. No. 32,537), Mark J. Abate (Reg. No. 32,527), John T. Gallagher (Reg. No. 35,516), Steven F. Meyer (Reg. No. 35,613), Kenneth H. Sonnenfeld (Reg. No. 33,285), Tony V. Pezzano (Reg. No. 38,271), Andrea L. Wayda (Reg. No. 43,979) and Walter G. Hanchuk Reg. No. (35,179) of Morgan & Finnegan, L.L.P. whose address is: 345 Park Avenue, New York, New York, 10154 and Michael S. Marcus (Reg. No. 31,727) and John E. Hoel (Reg. No. 26,279) of Morgan & Finnegan, L.L.P., whose address is 1775 Eye Street, Suite 400, Washington, D.C. 20006.

[ ]    I hereby authorize the U.S. attorneys and/or agents named hereinabove to accept and follow instructions from _____
_____ as to any action to be taken in the U.S. Patent and Trademark Office regarding this application without direct communication between the U.S. attorneys and/or agents and me. In the event of a change in the person(s) from whom instructions may be taken I will so notify the U.S. attorneys and/or agents hereinabove.

Full name of sole or first inventor     Randall L. BARBOUR

Inventor's signature*     _____     11/14/2000
                                                                              date

Residence     15 Cherry Lane, Glen Head, New York  11546   N Y

Citizenship     United States

Post Office Address     same


Full name of second joint inventor, if any     _____

Inventor's signature*     _____
                                                                              date

Residence     _____

Citizenship     _____

Post Office Address     _____

577200_1

Full name of third joint inventor, if any _____

Inventor's signature* _____

date

Residence _____

Citizenship _____

Post Office Address _____


[ ]     ATTACHED IS/ARE ADDED PAGE(S) TO COMBINED DECLARATION AND POWER OF
        ATTORNEY FORM FOR SIGNATURE BY FOURTH AND SUBSEQUENT INVENTORS

*  Before signing this declaration, each person signing must:

1.      Review the declaration and verify the correctness of all information therein; and

2.      Review the specification and the claims, including any amendments made to the claims.

After the declaration is signed, the specification and claims are not to be altered.

To the inventor(s):

The following are cited in or pertinent to the declaration attached to the accompanying application:

<u>Title 37, Code of Federal Regulation, § 1.56</u>

Duty to disclose information material to patentability.

(a)     A patent by its very nature is affect with a public interest. The public interest is best served, and the most effective patent examination occurs when, at the time an application is being examined, the Office is aware of and evaluates the teachings of all information material to patentability. Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the Office, which includes a duty to disclose to the Office all information known to that individual to be material to patentability as defined in this section. The duty to disclose information exists with respect to each pending claim until the claim is canceled or withdrawn from consideration, or the application becomes abandoned. Information material to the patentability of a claim that is canceled or withdrawn from consideration need not be submitted if the information is not material to the patentability of any claim remaining under consideration in the application. There is no duty to submit information which is not material to the patentability of any existing claim. The duty to disclose all information known to be material to patentability is deemed to be satisfied if all information known to be material to patentability of any claim issued in patent was cited by the Office or submitted to the Office in the manner prescribed by §§1.97(b)-(d) and 1.98. However, no patent will be granted on an application in connection with which fraud on the Office was practiced or attempted or the duty of disclosure was violated through bad faith or intentional misconduct. The Office encourages applicants to carefully examine:

(1)     prior art cited in search reports of a foreign patent office in a counterpart application, and

(2)    the closest information over which individuals associated with the filing or prosecution of a patent application believe any pending claim patentably defines, to make sure that any material information contained therein is disclosed to the Office.

Title 35, U.S. Code § 101

Inventions patentable

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Title 35 U.S. Code § 102

Conditions for patentability; novelty and loss of right to patent

A person shall be entitled to a patent unless –

(a)    the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent,

(b)    the invention was patented or described in a printed publication in this or foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States, or

(c)    he has abandoned the invention, or

(d)    the invention was first patented or caused to be patented, or was the subject of an inventor's certificate, by the applicant or his legal representatives or assigns in a foreign country prior to the date of the application for patent in this country on an application for patent or inventor's certificate field more than twelve months before the filing of the application in the United States, or

(e)    the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent, or

(f)    he did not himself invent the subject matter sought to be patented, or

(g)    before the applicant's invention thereof the invention was made in this country by another had not abandoned, suppressed, or concealed it. In determining priority of invention there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other ...

Title 35, U.S. Code § 103

Conditions for patentability; non-obvious subject matter

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having

-5-

ordinary skill in the art to which said matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

## Title 35, U.S. Code § 112 (in part)

Specification

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise and exact terms also enable any person skilled in the art to which it pertains, or with which it is mostly nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

## Title 35, U.S. Code § 119

Benefit of earlier filing date in foreign country; right of priority

An application for patent for an invention filed in this country by any person who has, or whose legal representatives or assigns have, previously regularly filed an application for a patent for the same invention in a foreign country which affords similar privileges in the case of applications filed in the United States or to citizens of the United States, shall have the same effect as the same application would have if filed in this country on the date on which the application for patent for the same invention was first filed in such foreign country, if the application in this country is filed within twelve months from the earliest date on which such foreign application was filed; but no patent shall be granted on any application for patent for an invention which had been patented or described in a printed publication in any country more than one year before the date of he actual filing of the application in this country, or which had been in public use or on sale in this country more than one year prior to such filing.

## Title 35, U.S. Code § 120

Benefit or earlier filing date in the United States

An application for patent for an invention disclosed in the manner provided by the first paragraph of section 112 of this title in an application previously filed in the United States, or as provided by section 363 of this title, which is filed by an inventor or inventors named in the previously filed application shall have the same effect, as to such invention, as though filed on the date of the prior application, if filed before the patenting or abandonment of or termination of proceedings on the first application or an application similarly entitled to the benefit of the filing date of the first application and if it contains or is amended to contain a specific reference to the earlier filed application.
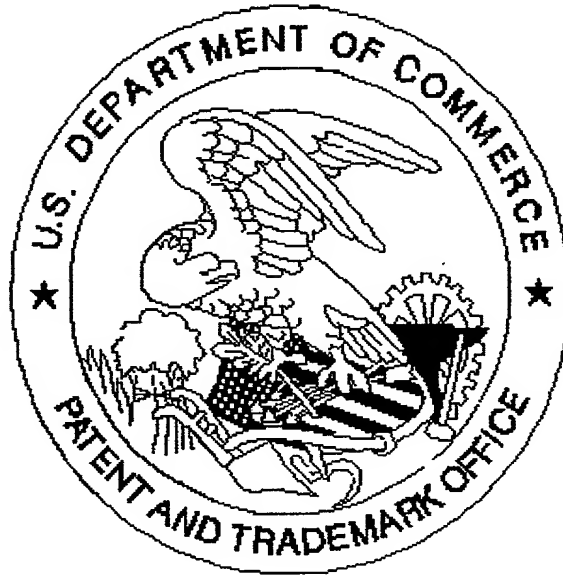
Please read carefully before signing the Declaration attached to the accompanying Application.

If you have any questions, please contact Morgan & Finnegan, L.L.P.

FORM:COMB-DEC.NY
Rev. 10/00

-6-

577200_1

# United States Patent & Trademark Office
## Office of Initial Patent Examination -- Scanning Division

Application deficiencies found during scanning:

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